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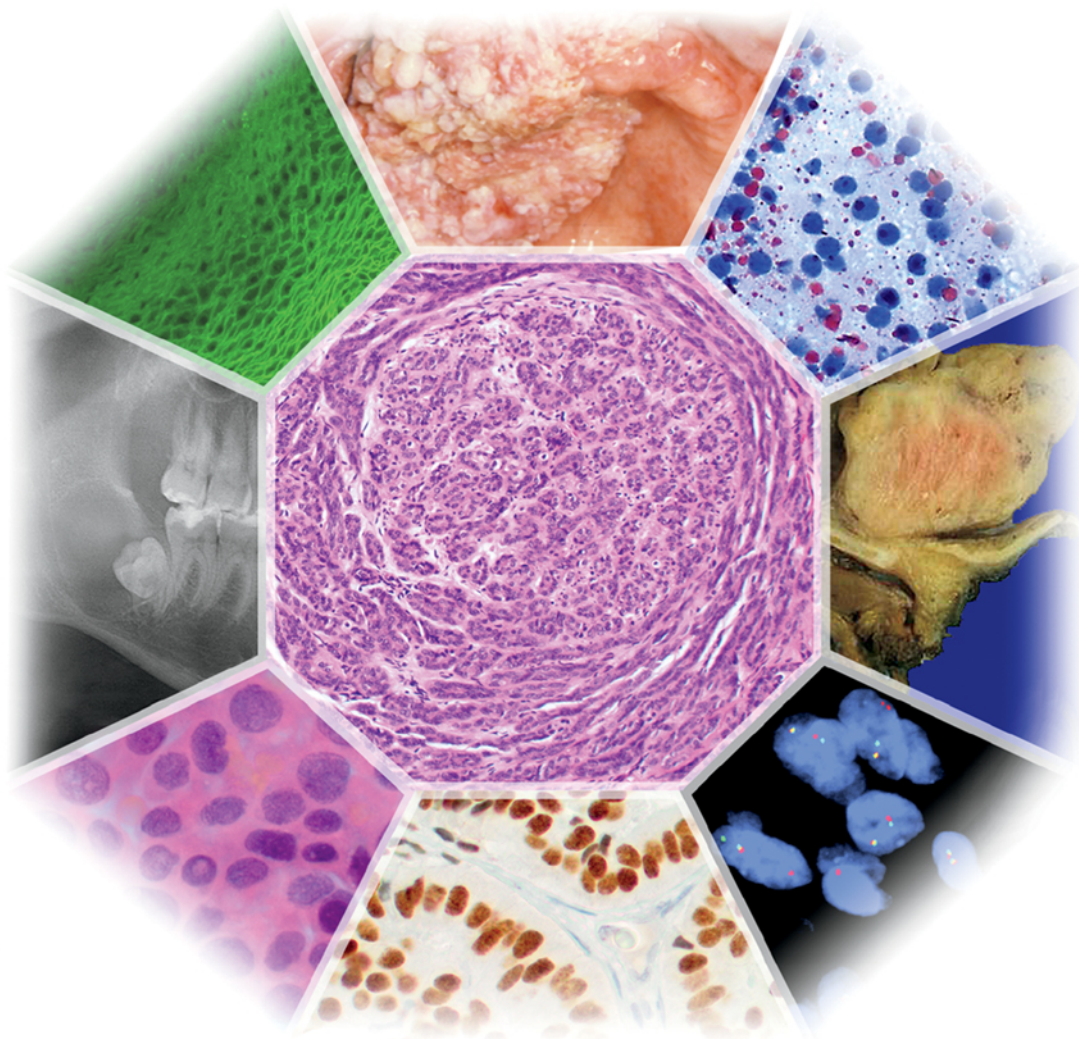
DIAGNOSTIC PATHOLOGY

Head & Neck

SECOND EDITION

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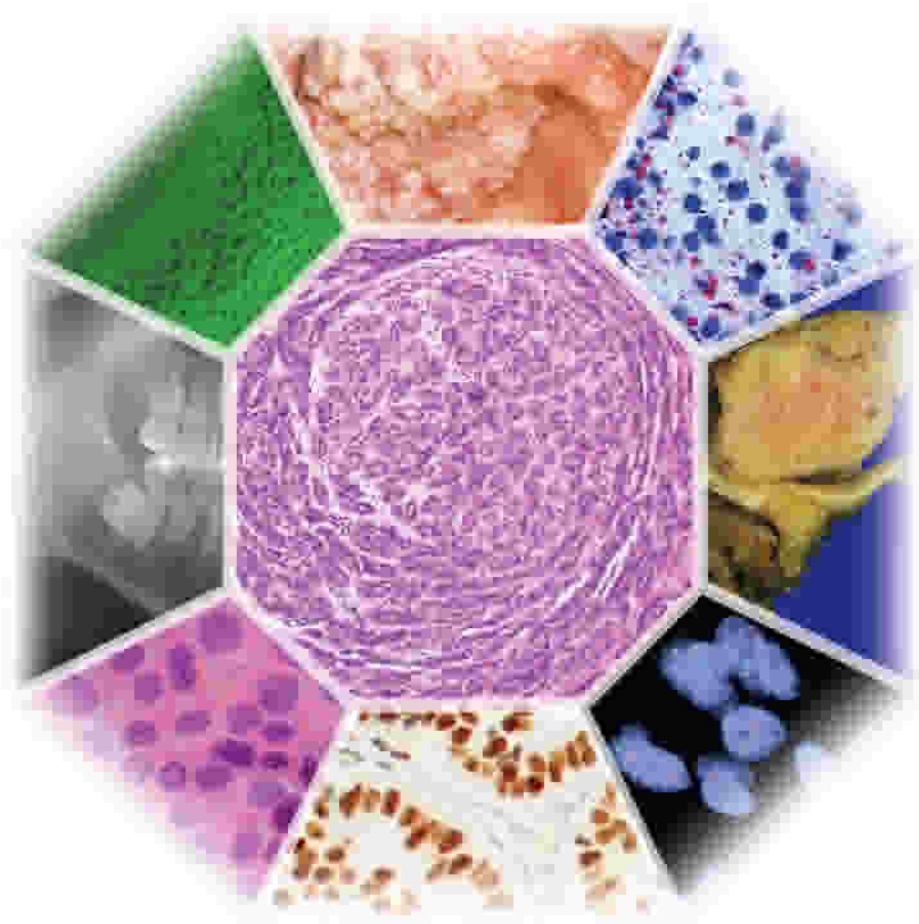
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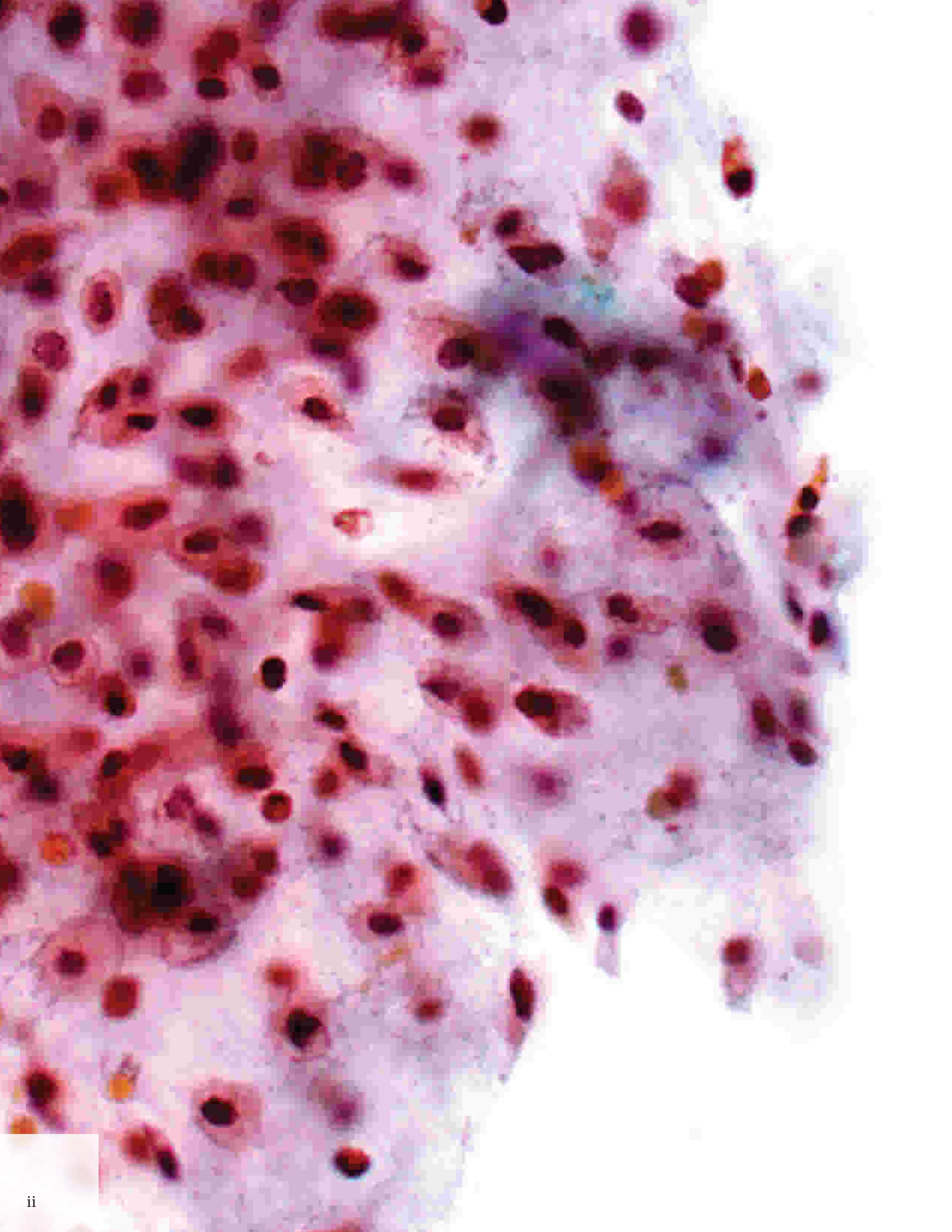
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DIAGNOSTIC PATHOLOGY

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Dedications

*A restaurant makes an interesting analogy to a hospital. The **maître d'** is the department secretary, eager to make sure you are welcome and made to feel at home. The reservations person is the scheduler who makes sure you got the table you wanted, with the people you expected at the correct time (like the technician to make sure specimens are matched to the right patient), have the correct orders, and the person requiring the results is listed. The waiters are the physicians who see where and how you are sitting, who you are sitting with, and gauge what you would like and dislike. They present you with a menu of potential disorders that you may try, carefully curating the exact tests you may need by individualizing your order to make certain you are going to get exactly what you want and need. They enter this information, based on table number and seat location, into the ordering system (i.e., electronic medical record) and then move on to the next customer/patient to start all over again. The bus staff are similar to nurses who make sure the things ordered are delivered and taken away appropriately, that you are made comfortable, and all of your requests and changes are communicated effectively. A sommelier is like the hospital administrator, a polished politician, groomed to tell you exactly what will make you feel better and to select the most luxurious and expensive plan offered.*

*All of the real action is in the kitchen: The **pathology** department. It is behind the scenes, an organized and heavily regimented grouping of tasks and functions. The conditions must be precise, temperatures controlled exactly, recipes (operating manuals) followed strictly, ingredients rigorously selected, properly mixed, and rigidly implemented. Each person in the kitchen has a uniquely specific roll, although, cross training and coverage is a plus. The kitchen stewards or scullery staff are those who do cleaning and washing, making certain the department is in good operating order. The kitchen hands, under direct chef supervision, are those involved in basic food preparation, the equivalent of tissue grossing and serial sectioning, tissue transfer, labeling, and dictating the exact findings.*

*The **commis chef** is essentially a resident/fellow, someone who is learning the ropes and working for a **chef de partie**. This can be a grueling and demanding job, making a person wonder if it will ever end. The **chef de partie** is a station or line chef, in charge of a specific area of the production. These folks are often the subspecialists, providing an extremely narrow but deep focus and an encyclopedic understanding of that field. A pastry chef is focused only on dessert, on making sure the last thing you have is wonderfully lingering so that you will always think fondly of your experience there. A **sous-chef** runs daily operations, a lab manager if you will. They schedule all of the work, organize the staff, keep inventory, and, in general, make sure that the food is out in a timely fashion. Finally, the **executive chef** is the person who takes all of the responsibility, designs the menu, manages the staff, and comes up with plating design. This is the person who writes the final report, carefully selects the order of the items, chooses a layout to highlight the features of interest, and finally puts their name on the report, or the final blessing before delivery. If they have done a good job, the customer/patient will ask their waiter/doctor to see the chef, who is then paraded out for a few minutes before returning to the solace and joy of cooking.*

*Everybody can find themselves within the roles of the restaurant. Thus, let me give specific thanks to my **maître d'**, Hannah B. Herrera, for always making sure everyone around me is comfortable, happy, and at ease (a wholly insurmountable task); to my **chefs de partie**, Brenda and Susan, who are always there for me; to my **pastry chef**, Dr. John Ohara, who made sure that everything was perfectly edited and consistent; and finally to my **executive chef**, Pam, the one who provided all and sacrificed much to achieve the whole.*

LDRT

To the most important person in my life, my wife Ana Maria, and to the most important people in our lives, our children Sarah, Eli, and Jake.

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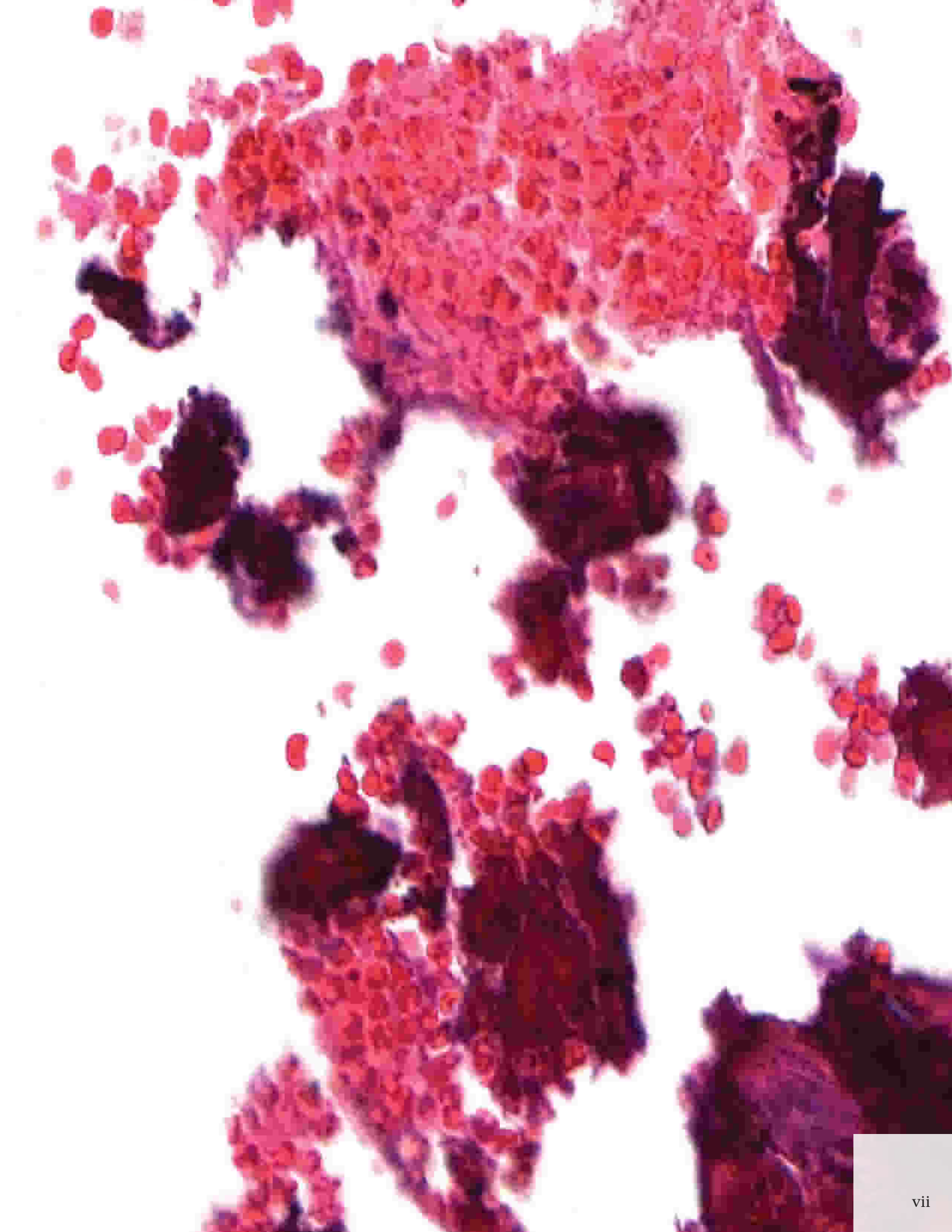
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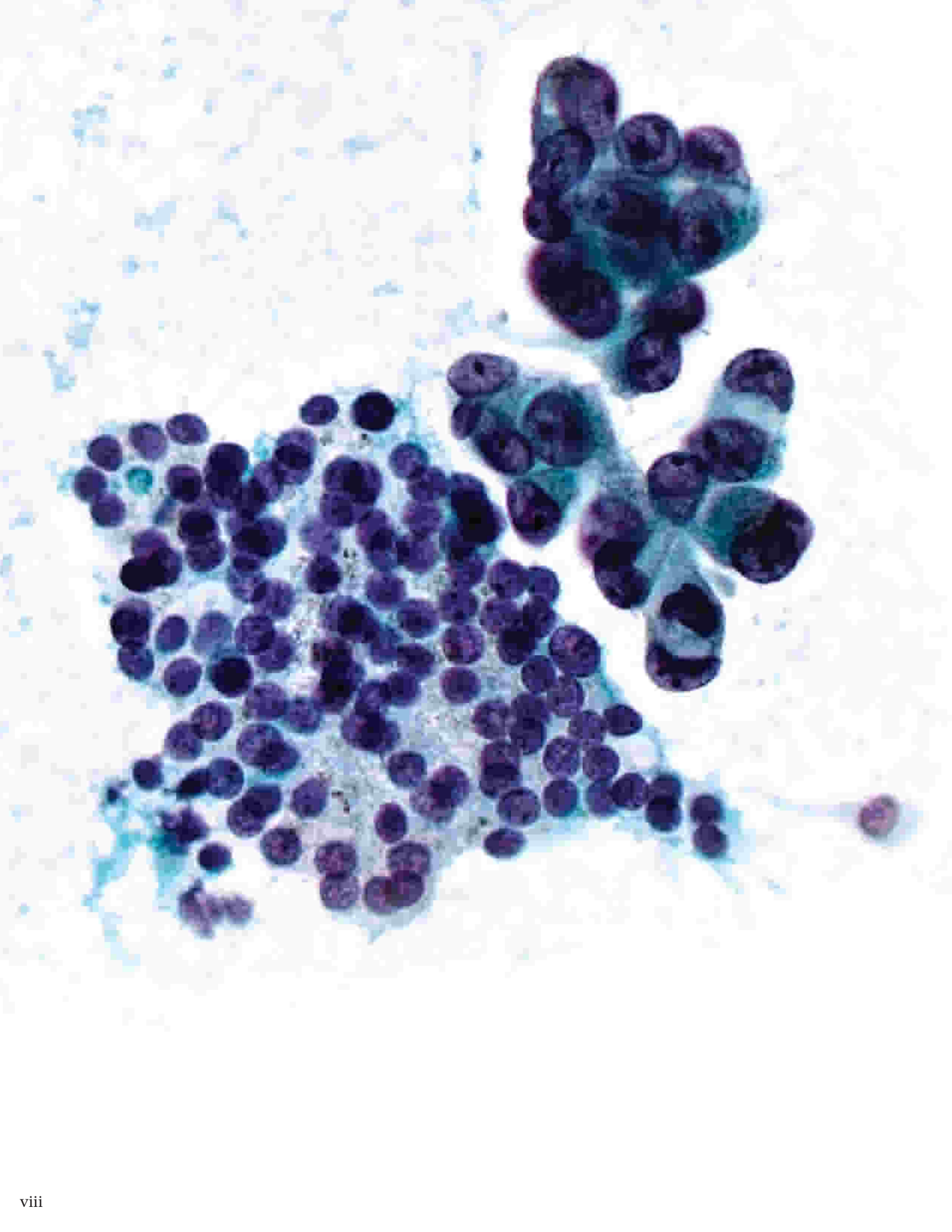
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Preface

The second edition of *Diagnostic Pathology: Head & Neck* has more than 1,100 pages organized into 10 sections, including Nasal Cavity and Paranasal Sinuses, Pharynx, Larynx and Trachea, Oral Cavity, Salivary Glands, Jaw, Ear and Temporal Bone, Neck, Thyroid Gland, and Parathyroid Glands. Each section begins with a short overview of the normal histology and anatomy of the site, followed by nonneoplastic lesions, benign and malignant neoplasms. The key facts and initial gallery of photographs allow for a quick reference of the topic. Presented in a highly templated and bulleted format, the 327 chapters include definitions, etiology, clinical and demographic parameters, treatment and prognosis, imaging findings, pathologic features (macroscopic, microscopic), ancillary studies (cytology, special stains, immunohistochemistry, molecular studies, genetics, and ultrastructure), and differential diagnoses. The reciprocal nature of the differential diagnoses was highlighted in this print edition but is also linked electronically to allow for easy comparison between entities. More than 4,300 illustrations and graphics are included in this book and the accompanying electronic version, highlighting diagnostic features and supporting findings for each entity.

Many new and unfolding entities are included, but due to the rapidly and constantly changing landscape of pathology, we know that information outdates quickly. To this end, the addition of these chapters to the ExpertPath collection allows us to keep this content fresh and relevant with ongoing updates.

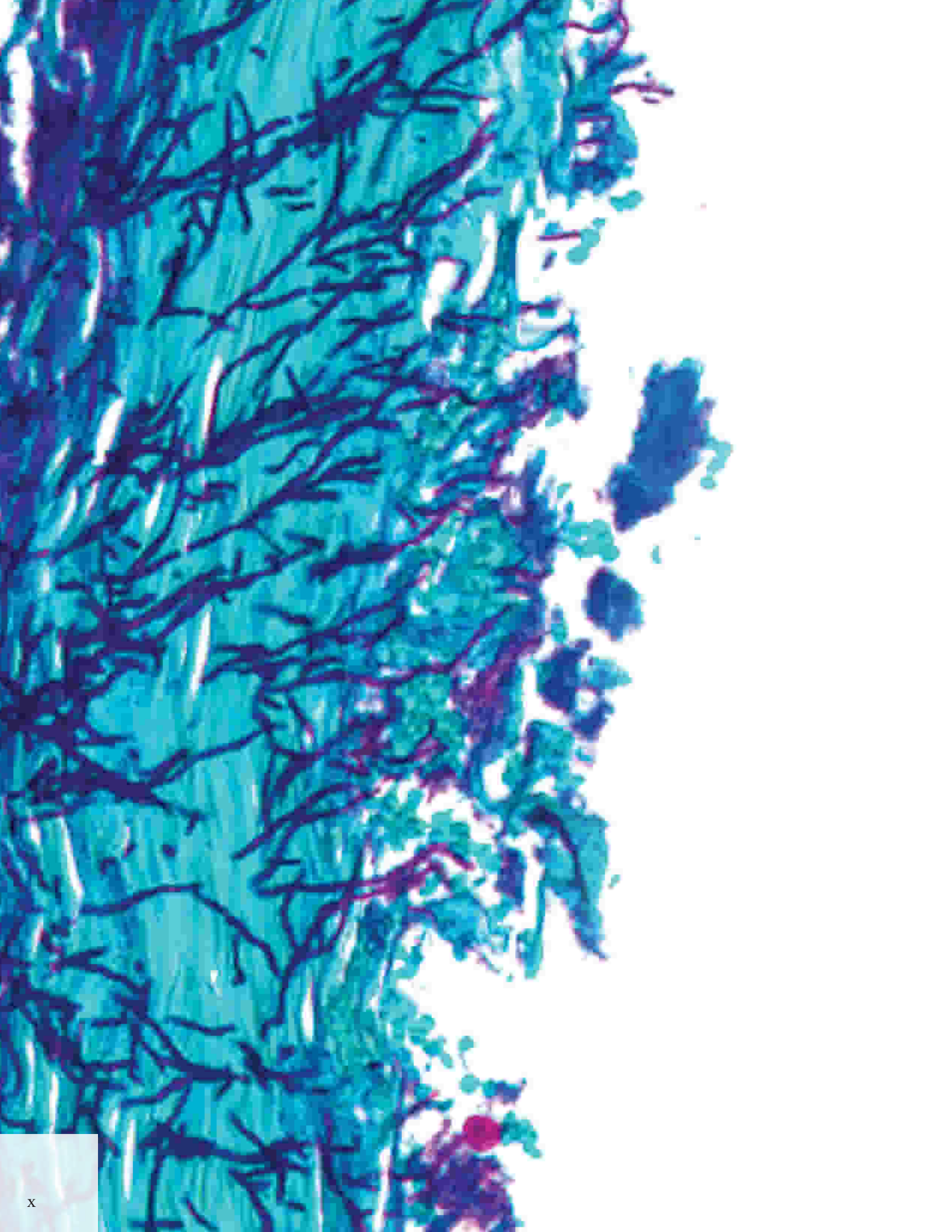
We hope that *Diagnostic Pathology: Head & Neck*, Second Edition will be a useful, practical, and valuable resource for individuals with interest in diseases of the head and neck.

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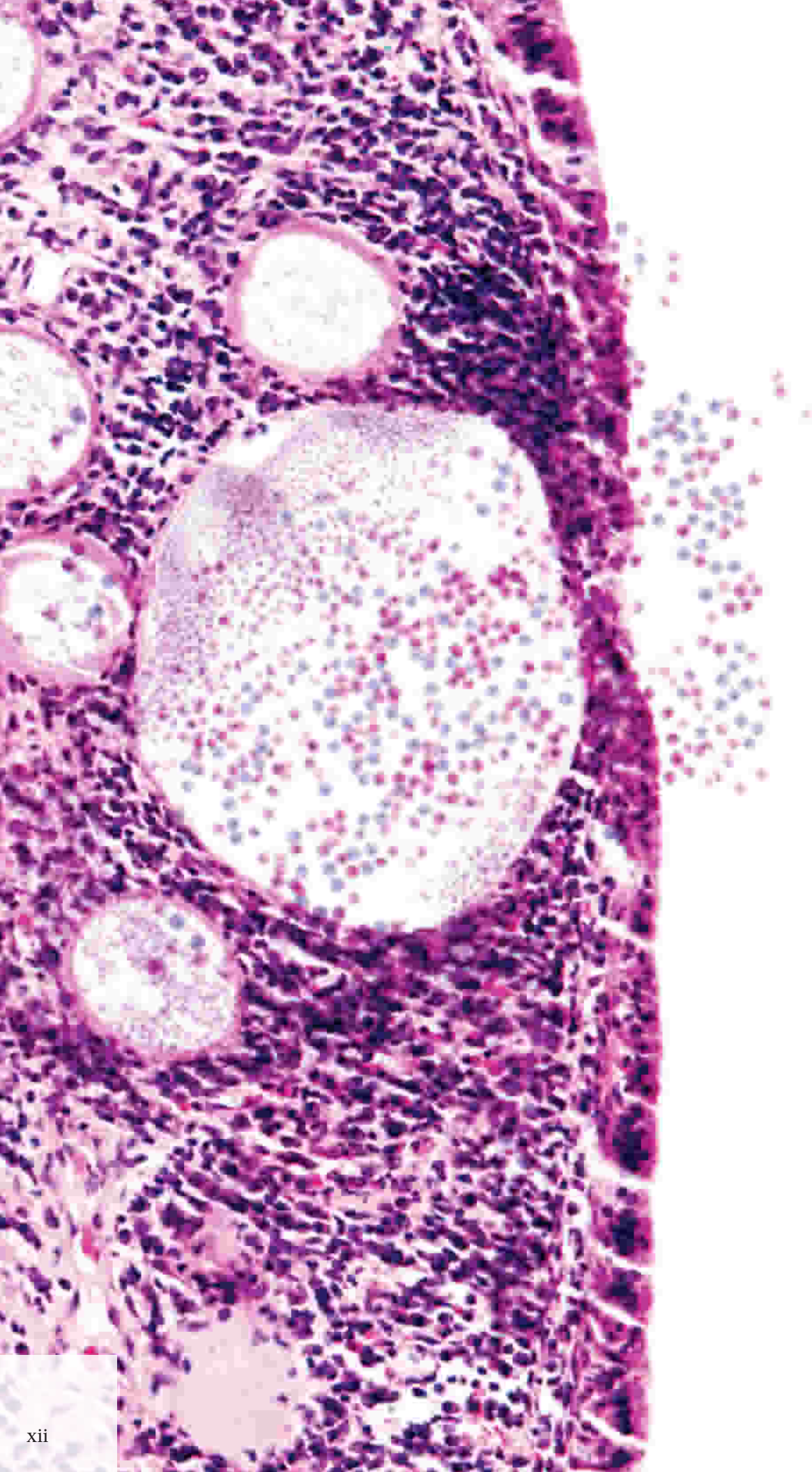
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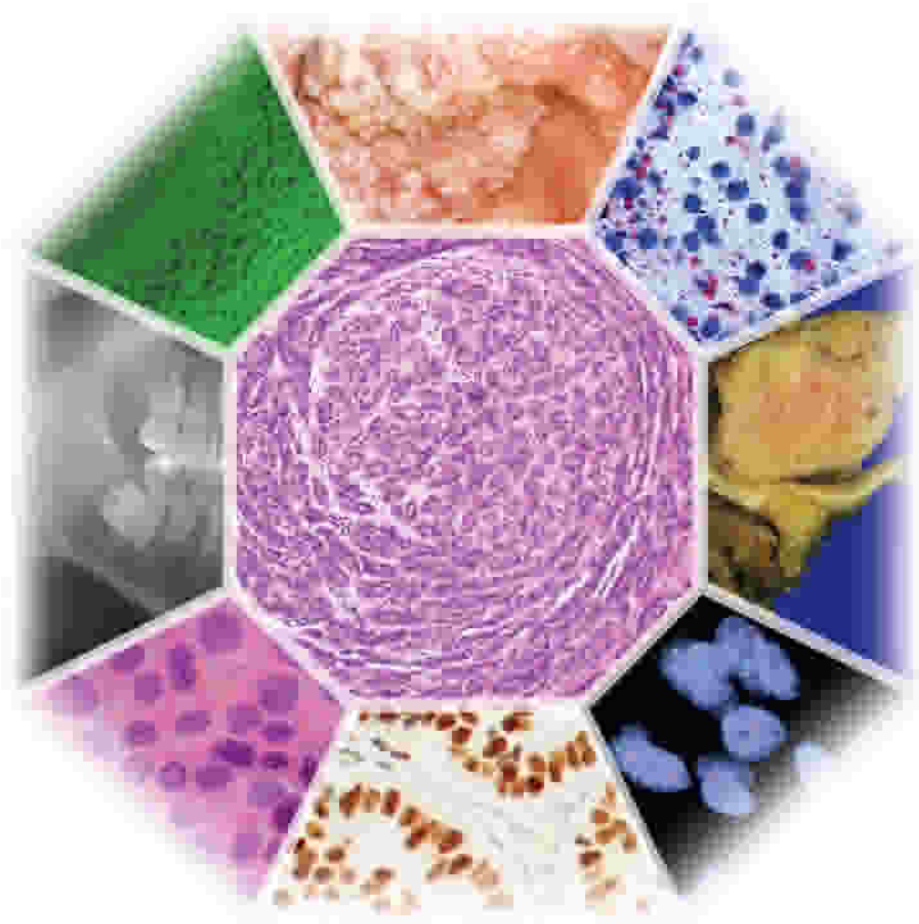
DIAGNOSTIC PATHOLOGY

Head & Neck

SECOND EDITION

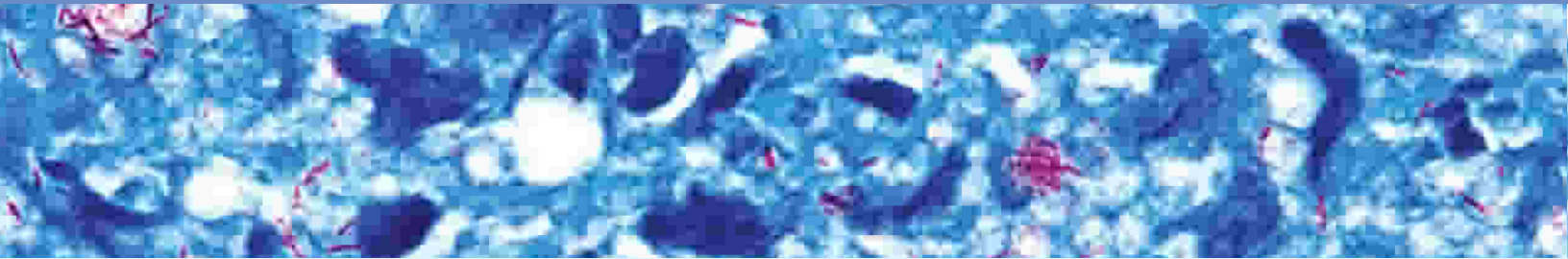
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MÜLLER • NELSON



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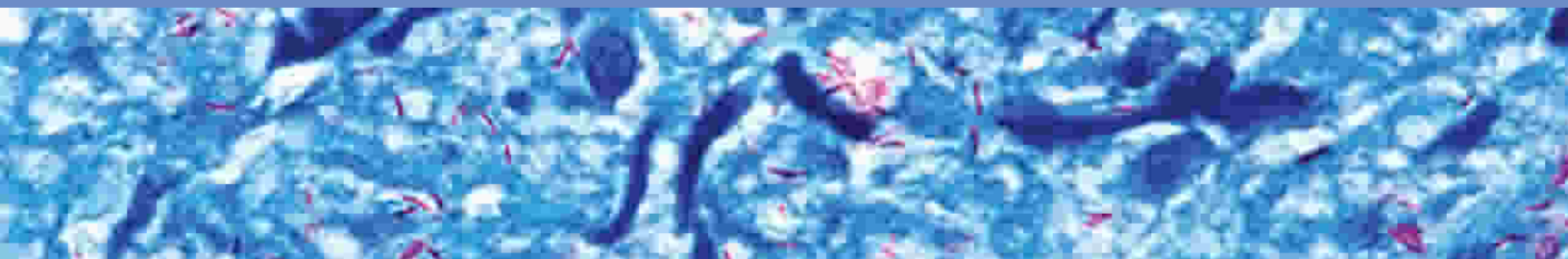
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MACROSCOPIC

Macroscopic Anatomy

- Paired nasal cavities extend anteriorly from nares (nostrils) and posteriorly to choanae, separated by nasal septum
 - Consist of 3 distinct regions: Vestibule, respiratory, and olfactory
- **Vestibule** communicates with external environment and contains hairs that act as coarse filter
- **Respiratory region** is most voluminous portion of nasal cavity
 - Medial wall is constituted by smooth nasal septum
 - Lateral wall contains 3 coiled bony projections called turbinates, which increase surface area and induce turbulence to inhaled air
 - Floor is smooth and sits on hard palate and anterior maxilla
- **Olfactory region** occupies majority of roof of nose and extends medially onto superior nasal septum and laterally onto superior portion of superior turbinate
- Paired air-filled paranasal sinuses include maxillary, frontal, ethmoid, and sphenoid sinuses
 - They communicate with, and are directly connected to, nasal cavity via ostia

MICROSCOPIC

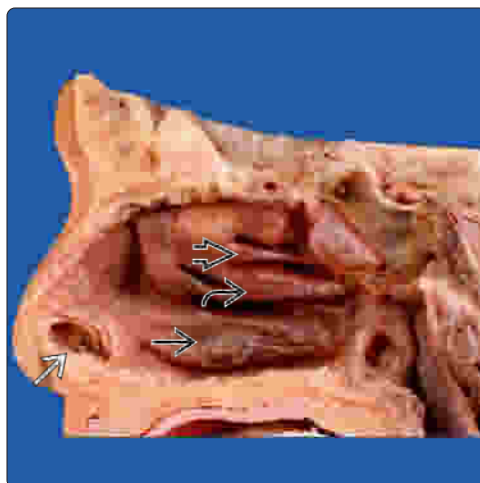
Microscopic Anatomy

- External nose is covered by epidermis with high concentration of sebaceous glands and fine hairs
- Vestibule consists of epidermis that is continuous with surface skin and contains sebaceous glands, sweat glands, and coarse hairs
- Majority of nasal cavity is lined by ciliated pseudostratified columnar respiratory epithelium
 - Epithelium is ectodermally derived from schneiderian membrane (referred to as schneiderian mucosa)
 - There is short transition of nonciliated columnar or transitional epithelium between vestibule and ciliated epithelium

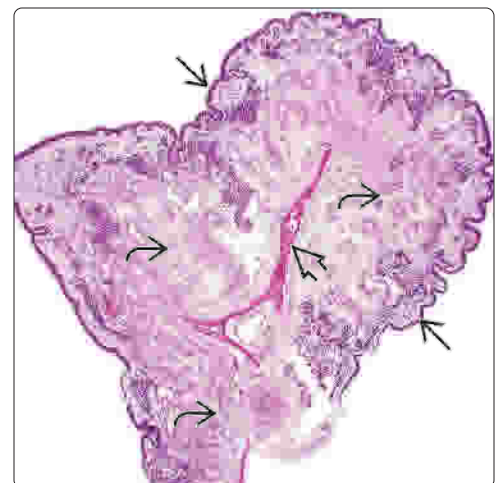
- 3 cell types are identifiable: Basal cells, goblet cells, and ciliated columnar cells
- Lamina propria contains numerous mucoserous glands, which drain to surface via small ducts
- Scattered melanocytes are present in surface mucosa, glands, and lamina propria
- Turbinates are lined by schneiderian epithelium but contain more prominent, specialized vascular component
 - Vessels form dense network of variably sized spaces resembling erectile tissue
 - Vessels have thick muscular walls and contract and dilate to regulate temperature and secretions
 - Osseous core consists of thin plates of lamellar bone with intraosseous vessels
- Nasal septum is composed of hyaline cartilage anteriorly, with remainder being plates of lamellar bone
 - Focal collection of ectatic thin-walled vessels can be seen on anterior cartilaginous portion (known as Kiesselbach or Little area)
- Olfactory mucosa is specialized sensory epithelium lined by ciliated pseudostratified columnar epithelium
 - 3 cell types are identifiable: Basal cells, ciliated columnar supporting/sustentacular cells, and olfactory neural cells
 - No goblet cells are present in olfactory region
 - Sustentacular cells may have lipofuscin pigment in older individuals
 - Olfactory neural cells are bipolar spindle cells with olfactory sense receptor cilia present on surface and axons at basal surface
 - Olfactory neural cells collect in lamina propria to form myelinated nerves that traverse cribriform plate to join olfactory nerve
 - Specialized serous secretory glands (glands of Bowman) are present in lamina propria and empty to surface via small ducts
- Sinuses are lined by schneiderian mucosa, but it is thinner, less vascular, and contains fewer mucoserous glands

(Left) The nasal vestibule ➡ communicates with the environment and contains coarse hairs. The lateral nasal wall contains superior ➡, middle ➡, and inferior ➡ turbinates. (Courtesy M. Nielsen, MS.) (Right) This cross section of a middle turbinate shows the delicate, curved bone core ➡ surrounded by thick lamina propria ➡, rich in variably sized vessels and covered by schneiderian mucosa ➡. Minor mucoserous glands are present.

Gross Anatomy of Lateral Nasal Cavity



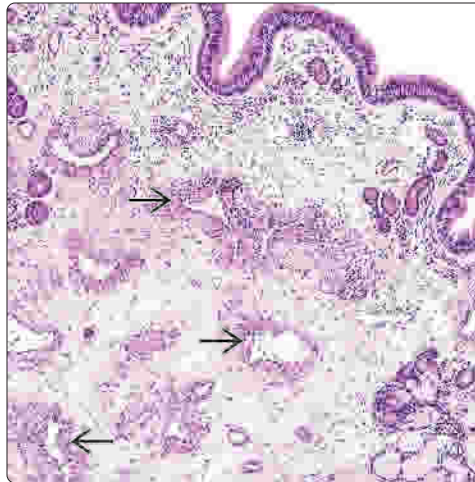
Histology of Middle Turbinate



Histology of Turbinate Bone



Turbinate Tissue Lamina Propria



(Left) Turbinate bone is composed of thin trabeculae of mature lamellar bone. There are numerous muscular veins, dilated vessels, and arteries that may mimic vascular neoplasms or malformations. Although there may be adipose tissue, no hematopoietic elements are present. (Right) The turbinate lamina propria contains a network of variably sized venous sinuses with thick muscular walls. These sinuses histologically resemble erectile tissue, rapidly constricting or dilating in response to various stimuli.

Histology of Nasal Vestibule



Histology of Respiratory Region



(Left) The nasal vestibule is lined by skin with stratified squamous epithelium containing all layers of normal epidermis. There are numerous hairs with associated sebaceous glands. The coarse hairs and secretions act to trap inhaled particulate matter. (Right) Mucoserous glands drain to the surface via small excretory ducts. The schneiderian epithelium is pseudostratified and columnar, containing cilia and scattered mucous (goblet) cells.

Histology of Olfactory Region



Olfactory Epithelium



(Left) Olfactory mucosa is a ciliated pseudostratified columnar mucosa with specialized intraepithelial olfactory nerve cells. These neurons fuse, forming olfactory nerve bundles. Specialized olfactory glands (Bowman glands) are unique. (Right) Olfactory epithelium contains bipolar olfactory nerve cells with nuclei stratified between the more uniform superficial nuclei of the ciliated columnar supporting (sustentacular) cells and the progenitor basal cells. No mucous cells are present.

Nasal Glial Heterotopia

KEY FACTS

TERMINOLOGY

- Nasal glial heterotopia are congenital malformations of displaced normal, mature glial tissue (choristomas)
- Encephalocele represents herniation of brain tissue and leptomeninges through bony defect of skull

CLINICAL ISSUES

- NGH usually presents during infancy
- Separated into 2 types, based on location
- Extranasal (60%): Subcutaneous bridge of nose
- Intranasal (30%): Superior nasal cavity
- Firm, subcutaneous nodule at bridge of nose
- Obstruction, nasal polyps, chronic rhinosinusitis, nasal drainage
- Radiographs are prerequisite to avoid postbiopsy complications, including meningitis and CSF rhinorrhea
- Excellent outcome with surgery, although recurrences occur (up to 30%) if incompletely excised

MICROSCOPIC

- Skin or surface mucosa is intact
- Fibrous connective tissue blended with glial tissue
- Fibrosis frequently obliterates or obscures glial tissue; special stains required to confirm
- Prominent glial fibrillar network
- Gemistocytes may be noted



ANCILLARY TESTS

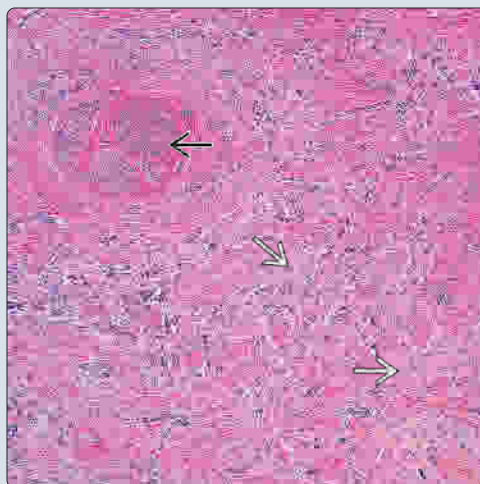
- Trichrome: Glial tissue is bright red; fibrosis is blue
- Glial tissue is highlighted with S100 protein and GFAP (latter more sensitive)

TOP DIFFERENTIAL DIAGNOSES

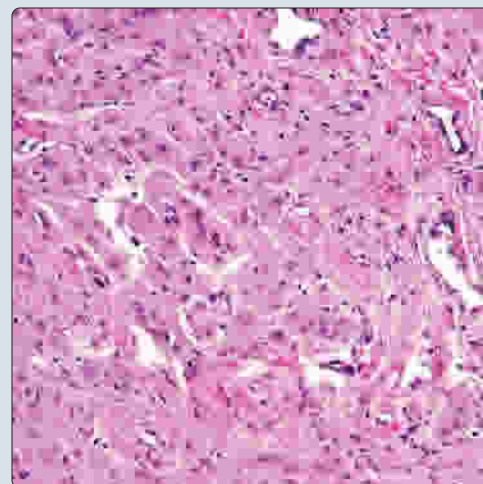
- Fibrosed nasal polyp: Lacks glial tissue, contains mucoserous glands, and usually has greater amount of inflammation

Glial Tissue Blended With Fibrosis


(Left) The glial tissue  identified as part of nasal glial heterotopia can be very challenging to separate from the adjacent fibrous connective tissue that is a common component of the lesion. Note the peripheral nerve  intermixed with the proliferation. (Right) Hematoxylin & eosin shows the intermingling of glial elements with fibrosis. This is a very subtle finding, highlighting the reason for performing special studies in many cases.

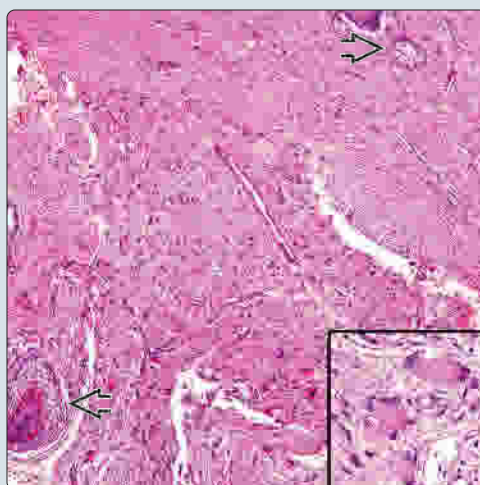


Glial Tissue in Fibrosis

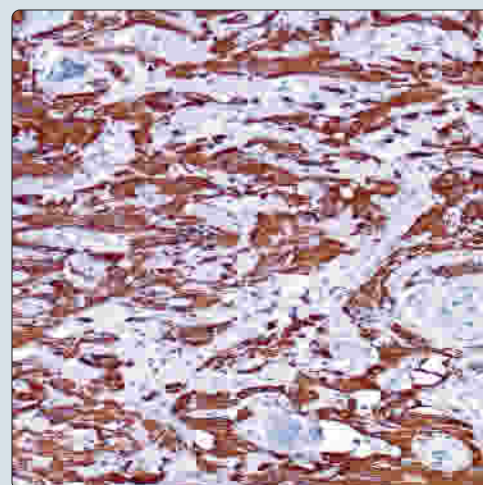


Gemistocytic-Like Glial Cells in Fibrosis

(Left) Hematoxylin & eosin shows pilosebaceous units  with a gemistocytic-like glial proliferation within the fibrous connective tissue. The tissue often extends into the dermis or subcutaneous tissue. The inset shows higher power of the gemistocytes. (Right) GFAP strongly and diffusely highlights the neural tissue in this example of nasal glial heterotopia. The fibrous connective tissue is negative.



GFAP Strongly Highlights Neural Tissue



TERMINOLOGY

Abbreviations

- Nasal glial heterotopia (NGH)

Synonyms

- Glioma: Implies tumor and is to be discouraged

Definitions

- Nasal glial heterotopia are congenital malformations of displaced normal, mature glial tissue (choristomas)
- Encephalocele represents herniation of brain tissue and leptomeninges through bony defect of skull

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Congenital malformation of displaced normal and mature glial tissue

Iatrogenic

- Encephalocele is herniation of brain tissue through bony defect
 - Often secondary to infections, trauma, or surgery

CLINICAL ISSUES

Epidemiology

- Incidence
 - NGH is rare, while encephalocele is uncommon
- Age
 - NGH usually presents during infancy
 - Encephalocele may present in older children and adults
- Sex
 - Equal gender distribution

Site

- Separated into 2 types, based on location
 - Extranasal (60%): Subcutaneous bridge of nose
 - Intranasal (30%): Superior nasal cavity
 - Mixed (10%)

Presentation

- Firm, subcutaneous nodule at bridge of nose
- Polypoid mass within superior nasal cavity
- Obstruction, nasal polyps, chronic rhinosinusitis, nasal drainage
- Chronic otitis media
- CSF rhinorrhea represents encephalocele

Treatment

- Excision must be adequate

Prognosis

- Excellent, with recurrences (up to 30%) if incompletely excised

IMAGING

Radiographic Findings

- Radiographs are prerequisite to avoid postbiopsy complications, including meningitis and CSF rhinorrhea
- Sharply demarcated, expansile mass
- Need to document continuity with central nervous system

- Intracranial extension (tract or cribriform plate defect) must be excluded
 - Especially difficult to document with CT or MR if defect is small

MACROSCOPIC

General Features

- Smooth, homogeneous glistening cut surface, similar to brain tissue
- Sometimes fibrous connective tissue dominates, making it firm

Size

- Usually < 2 cm

MICROSCOPIC

Histologic Features

- Skin or surface mucosa is intact
- Glial tissue appears similar to gliosis
- Fibrous connective tissue blended with glial tissue
 - Fibrosis frequently obliterates or obscures glial tissue; special stains required to confirm
- Nests and sheets of fibrillar neuroglial tissue
- Prominent glial fibrillar network
- Gemistocytes may be noted, while neurons are uncommon
- Choroid plexus, ependyma, and retinal pigmented cells are exceedingly rare
- Encephalocele shows glial degeneration but requires radiographic/clinical correlation

ANCILLARY TESTS

Histochemistry

- Trichrome: Glial tissue is bright red; fibrosis is blue

Immunohistochemistry

- Glial tissue **positive** with S100 protein and GFAP (latter more sensitive)

DIFFERENTIAL DIAGNOSIS

Fibrosed Nasal Polyp

- Lacks glial tissue, contains mucoserous glands, and usually has greater amount of inflammation

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Nasal Dermoid Cyst and Sinus

KEY FACTS

TERMINOLOGY

- Congenital developmental lesion virtually identical to dermoid cysts found in other anatomic locations

ETIOLOGY/PATHOGENESIS

- May be associated with or coexist with other congenital developmental malformations
- May be familial

CLINICAL ISSUES

- Represent ~ 10% of all dermoids in cervicofacial region
- Usually infants or young children
- Majority occur at root of nose (nasal bridge) although may be found in lower and lateral regions of nose near nasal ala
- Preoperative evaluation essential to rule out intracranial extension
 - Delineate deep tissue involvement
 - Exclude possible associated intracranial extension
 - Necessary to assess deep extent of lesion

- Surgery is curative treatment
- Most important treatment concern is possibility of associated deeply seated cyst or related sinus tract involving anterior midline skull base
- Radiographic examination to assess deep extent of lesion is obviously important in planning operative removal

MICROSCOPIC

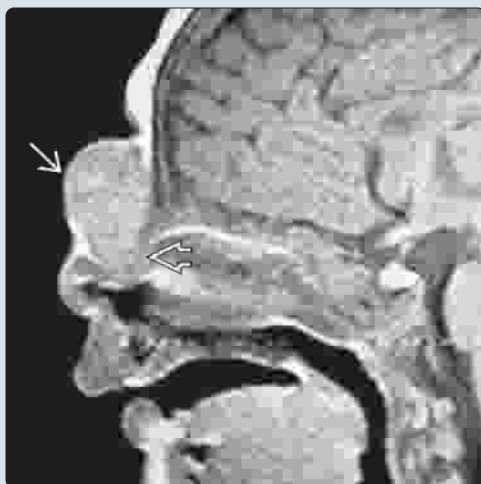
- Stratified squamous epithelium lines cyst with cutaneous appendages including
 - Hair follicles, sebaceous glands, sweat glands identified in connective tissue wall

TOP DIFFERENTIAL DIAGNOSES

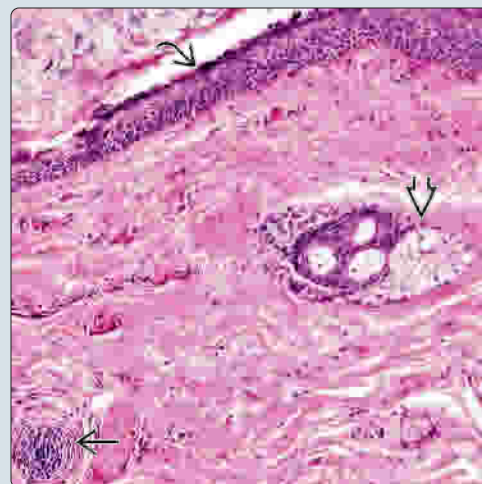
- Normal skin surface
- Nasopharyngeal dermoids
- Nasal glial heterotopia

MR of Nasal Dermoid

(Left) Sagittal T1WI MR shows large intermediate signal midline nasal mass without an intracranial connection consistent with extranasal glioma. Notice bowing of the nasal bridge inward. (Right) The resected cystic lesion is lined by stratified squamous epithelium with identifiable cutaneous appendages, including sebaceous glands and hair follicles in the wall of the cyst.

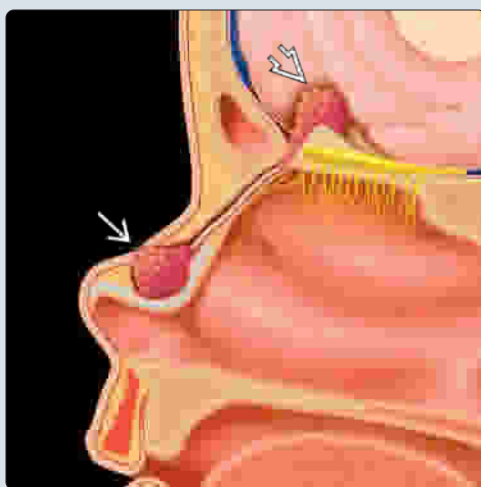


Histology of Nasal Dermoid

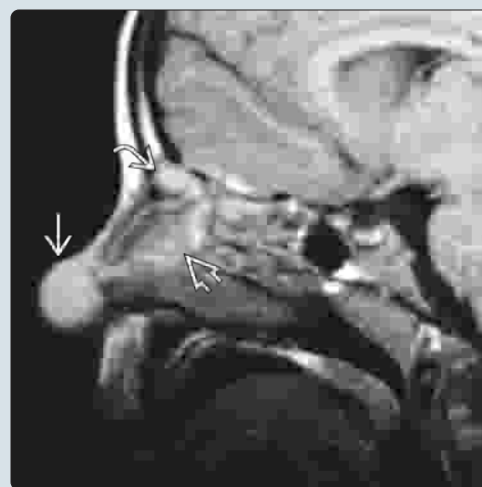


Graphic Image of Sinus With CNS Extension

(Left) Sagittal graphic depicts nasal dermal sinus with extracranial dermoid just below the nasal pit; an intracranial dermoid splits bifid crista galli. (Right) Sagittal T1WI MR shows the dermoid at the nasal tip. Additional dermoids are noted in the nasal septum and at the skull base.



MR Showing Multiple Nasal Dermoids



TERMINOLOGY

Synonyms

- Craniofacial dermoid

Definitions

- Congenital developmental lesion histologically identical to dermoid cysts found in other anatomic locations

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- May be associated with or coexist with other congenital developmental malformations
- May be familial
- Predominance as midline lesion on nasal bridge
 - Similar location as glial heterotopias suggests relationship between these lesions

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~ 10% of all dermoids in cervicofacial region
- Age
 - Usually infants or young children
 - May occur in adults
- Sex
 - Equal gender distribution

Site

- Majority occur at root of nose (nasal bridge), although may be found in lower and lateral regions of nose near nasal ala
 - Small lesions or deeply seated cysts may not be apparent until after they become infected and inflamed
 - Sinus tract with epidermal opening may be present
 - Intracranial extension may occur
 - Rarely, may present with median upper lip fistula

Presentation

- Midline swelling

Treatment

- Options, risks, complications
 - Most important treatment concern is possibility of associated deeply seated cyst or related sinus tract involving anterior midline skull base
 - Radiographic examination to assess deep extent of lesion is obviously important in planning operative removal
- Surgical approaches
 - Lesions with intracranial extension have traditionally been managed with
 - Lateral rhinotomy
 - Midface degloving
 - External rhinoplasty combined with frontal craniotomy
 - More recently, subcranial approach proposed
 - Offers excellent exposure
 - Minimizes frontal lobe retention
 - Reduces likelihood of cerebrospinal fluid leak
 - Provides for excellent cosmetic result

- Shows long-term follow-up with no recurrence or negative effect on craniofacial growth

Prognosis

- Surgery is curative treatment
- Low recurrence rates

IMAGING

Radiographic Examination

- Preoperative evaluation essential to rule out intracranial extension
- CT &/or MR indicated in order to
 - Delineate deep tissue involvement
 - Exclude possible associated intracranial extension
- Necessary to assess deep extent of lesion

MACROSCOPIC

General Features

- Small lesions or deeply seated cysts may not be apparent until after they become infected and inflamed
- Sinus tract with epidermal opening may be present
- Intracranial extension may occur

MICROSCOPIC

Histologic Features

- Stratified squamous epithelium lines cyst with cutaneous appendages identified in connective tissue wall including
 - Hair follicles
 - Sebaceous glands
 - Sweat glands
- Lumen filled with keratin or sebaceous material
- Respiratory epithelium may be identified

DIFFERENTIAL DIAGNOSIS

Normal Skin Surface

- Clinical presentation as mass or swelling assists in differentiating dermoid cyst from normal skin

Nasopharyngeal Dermoids

- Not actually cysts but ectopic accessory auricles

Nasal Glial Heterotopia

- Glial tissue identified
 - Confirmed by immunohistochemical staining including
 - Glial fibrillary acidic protein (GFAP)
 - Neurofibrillary protein (NFP)

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Primary Ciliary Dyskinesia

KEY FACTS

TERMINOLOGY

- Multisystem disease caused by ultrastructural defects of respiratory cilia and sperm tails characterized by
 - Recurrent respiratory tract infections, sinusitis, bronchiectasis, and male subfertility, associated in ~ 50% patients with situs inversus totalis

ETIOLOGY/PATHOGENESIS

- Usually inherited as autosomal recessive trait
- Majority are inherited as autosomal recessive trait, but pedigrees showing autosomal dominant or x-linked recessive modes of inheritance have been reported
- Ciliary gene mutations are now known to cause single organ disease, as well as complex syndromes
- Different genes are involved in different patients and genetic mutations

CLINICAL ISSUES

- Majority of cases are congenital due to inborn genetic error

- Typically presents in early neonatal period
- Characterized by recurrent respiratory tract infections, sinusitis, bronchiectasis, and male subfertility
 - Sinusitis, mucopurulent rhinorrhea, otitis media often striking, occurring in virtually all patients
- Chronic bronchitis, recurrent pneumonia, and atelectasis virtually pathognomonic for Kartagener syndrome

MACROSCOPIC

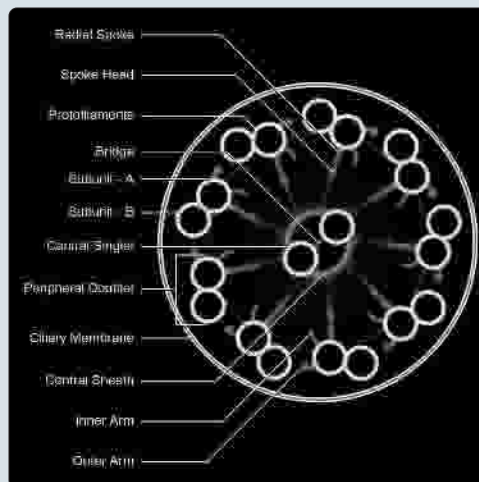
- Nasal cavity biopsy is usually most easily obtained specimen

ANCILLARY TESTS

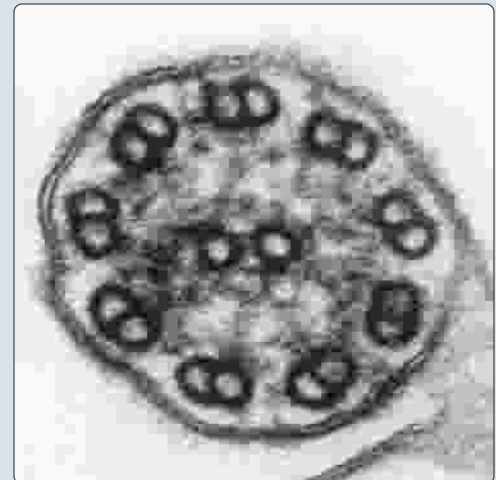
- Absence of dynein arms is most confidently diagnosable structural anomaly
- Ultrastructural exam is unreliable as sole criteria for definitive diagnosis
- Combining ultrastructural analysis and molecular genetics increases diagnostic yield

Schematic Image of Normal Cilia

(Left) Schematic cross section of a ciliary axoneme (main body of the organelle) details the normal ciliary structures, including single central couplet and 9 pairs of peripheral doublets. (Right) Electron microscopic evaluation of nasal biopsy in a patient suspected of having primary ciliary dyskinesia (PCD) shows a cilia with complete absence of dynein arms, the most confidently diagnosable ciliary structural anomaly.

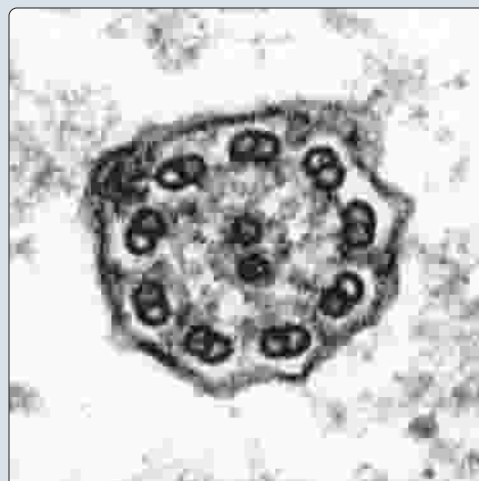


Complete Absence of Dynein Arms



Cilia in Kartagener Syndrome

(Left) Patient with known Kartagener syndrome (situs inversus totalis) shows the absence of dynein arms. Evaluation of cilia is not required in a patient known to have Kartagener syndrome. (Right) In this case, there is a partial absence of inner and outer dynein arms. It is important to not overinterpret dynein arm structural abnormalities if the cilia are not sectioned perpendicular.



Partial Absence of Dynein Arms



TERMINOLOGY

Abbreviations

- Primary ciliary dyskinesia (PCD)

Synonyms

- Immotile cilia syndrome

Definitions

- Multisystem disease caused by ultrastructural defects of respiratory cilia and sperm tails characterized by
 - Recurrent respiratory tract infections, sinusitis, bronchiectasis, and male subfertility, associated in ~ 50% patients with situs inversus totalis

ETIOLOGY/PATHOGENESIS

Genetic

- Majority are inherited as autosomal recessive trait, but pedigrees showing autosomal dominant or x-linked recessive modes of inheritance have been reported
- PCD-causing mutations have been identified in 20 genes, but collectively they account for only ~ 65% of all PCDs
- Ciliary gene mutations are now known to cause single organ disease, as well as complex syndromes
- Different genes are involved in different patients and genetic mutations; some include
 - Loss-of-function mutations in *ARMC4* cause PCD with situs inversus and cilia immotility, associated with loss of distal outer (but not inner) dynein arms
 - Mutations in *SPAG1* cause PCD with ciliary outer dynein arm and inner dynein arm defects
 - *RSPH1* mutations appear as major etiology for PCD phenotype including central complex and radial spoke defects

Acquired

- Referred to as secondary ciliary dyskinesia, usually result of epithelial alterations subsequent to inflammatory disease

CLINICAL ISSUES

Epidemiology

- Incidence
 - Unknown
 - Associated in ~ 50% of patients with situs inversus totalis (Kartagener syndrome)
- Age
 - Typically presents in early neonatal period

Presentation

- Ciliopathies are a category of diseases caused by disruption of physiological functions of cilia
- Characterized by recurrent respiratory tract infections, sinusitis, bronchiectasis, and male subfertility
 - Sinusitis, mucopurulent rhinorrhea, otitis media often striking, occurring in virtually all patients
- Chronic bronchitis, recurrent pneumonia, and atelectasis virtually pathognomonic for Kartagener syndrome

Laboratory Tests

- Exhaled and nasal nitric oxide (NO) measurements useful to screen children and detect PCD in children

Treatment

- Palliative, centered on maintaining airway
- Surgery may be required for nasal polyps

Prognosis

- Not usually life-threatening
- Ciliary abnormality represents universal and permanent genetic defect
- Early recognition and initiation of both otolaryngologic and pulmonary management might reduce potential long-term morbidities

MACROSCOPIC

Sections to Be Submitted

- Nasal cavity biopsy most easily obtained specimen
- Tracheal mucosal brushing or biopsy has much higher chance of producing specimen with abundant cilia

ANCILLARY TESTS

Electron Microscopy

- Ultrastructural examination of cilia required for diagnostic purposes
 - Absence of dynein arms is most confidently diagnosable structural anomaly
 - Dynein arms necessary for translational movement of ciliary peripheral doublet tubules with respect to one another
- Ultrastructural exam is unreliable as sole criteria for a definitive diagnosis
 - Combining ultrastructural analysis and molecular genetics increases diagnostic yield

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KEY FACTS

TERMINOLOGY

- Eosinophilic fungal rhinosinusitis (EFRS)
- Allergic response within sinonasal tract mucosa to aerosolized fungal allergens, amplified and perpetuated by eosinophils

ETIOLOGY/PATHOGENESIS

- Allergic reaction to inhaled fungal elements
- *Aspergillus* species most common

CLINICAL ISSUES

- Atopy is common (allergy)
- Polyps with putty-like material
- Peripheral eosinophilia
- Elevated fungal-specific IgE
- Extensive debridement and complete evacuation of impacted mucin is mainstay of therapy
- Postoperative anti-inflammatory therapy, including oral corticosteroids

MACROSCOPIC

- Foul odor
- Putty or crunchy peanut butter-like consistency
- Muddy or greasy consistency

MICROSCOPIC

- "Tide lines," "tree rings," waves, or ripples of mucin material alternating with inflammatory debris
- Charcot-Leyden crystals (degenerated eosinophils)

ANCILLARY TESTS

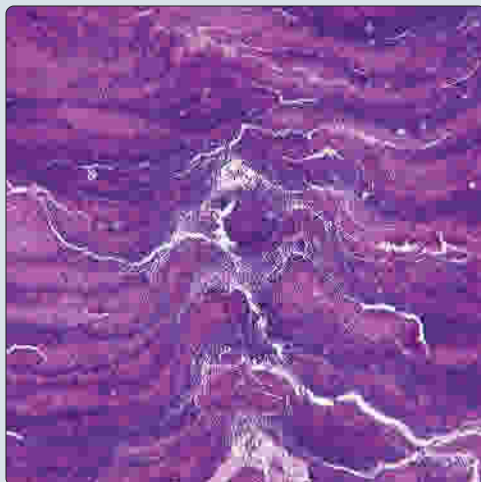
- PAS-D easier to interpret
- Gomori methenamine silver (GMS)

TOP DIFFERENTIAL DIAGNOSES

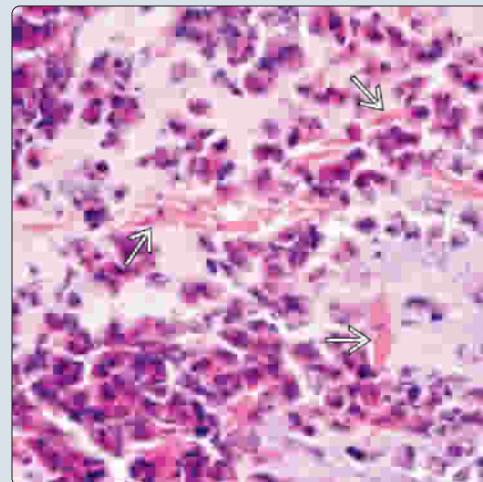
- Invasive fungal sinusitis
- Mycetoma

Characteristic H&E "Tide Lines"

(Left) Hematoxylin & eosin shows "tide lines," "tree rings," or alternating bands of nuclear and cytoplasmic debris, findings characteristic for allergic fungal sinusitis. (Right) Hematoxylin & eosin shows degenerated inflammatory cells and eosinophils with Charcot-Leyden crystals (breakdown products of eosinophils).



Charcot-Leyden Crystals



Computed Tomography Scan of AFS

(Left) Radiologic image shows opacification but no destruction of the left nasal cavity and sinuses by allergic fungal sinusitis. Polyps are noted in the contralateral maxillary sinus, a frequent concurrent finding. (Right) Gross photograph shows a polypoid fragment of tissue with multiple projections. The tissue was greasy with a putty-like consistency on cut section.



Gross: Polyp With Putty Appearance



TERMINOLOGY

Abbreviations

- Allergic fungal sinusitis (AFS)

Synonyms

- Allergic mucin
- Eosinophilic fungal rhinosinusitis (EFRS)
- Eosinophilic mucin rhinosinusitis (EMRS)
- Allergic fungal rhinosinusitis
- Hypertrophic sinus disease (HSD)
- Atopical fungal sinusitis

Definitions

- Allergic response in sinonasal tract mucosa to aerosolized fungal allergens, amplified and perpetuated by eosinophils

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Allergic reaction to inhaled fungal elements
 - Class II genes in major histocompatibility complex are involved in antigen presentation and immune response/modulation
 - Allergic reaction develops in immunocompetent people
 - *Aspergillus* species most common
 - Dematiaceous (brown-pigmented) fungi
 - Widespread in soil, wood, and decomposing plant material
 - *Alternaria*
 - *Bipolaris*
 - *Curvularia*
 - *Exserohilum*
 - *Phialophora* species
 - *Mucor* is uncommon agent

Pathogenesis

- Atopic host is exposed to finely dispersed fungi
- Inflammatory response is mediated by immunoglobulin E (IgE)
 - Type 1 hypersensitivity reaction
- Tissue edema with sinus obstruction and stasis
- Proliferation of fungus results in increased antigenic exposure
- Self-perpetuating cycle producing allergic mucin and possibly polyps

CLINICAL ISSUES

Epidemiology

- Incidence
 - Common
 - Approximately 10% of patients with chronic rhinosinusitis or nasal polyposis have AFS concurrently
 - Increased frequency in patients with asthma, allergies (atopy), and allergic bronchopulmonary aspergillosis (ABPA)
 - Increased in warmer climates
- Age
 - Usually in 3rd to 7th decades
 - Not a disease seen in children
- Sex

- Equal gender distribution
 - Males more likely to present with bone erosion than females

Site

- Nasal cavity
- Paranasal sinuses
 - Maxillary and ethmoid sinuses most common

Presentation

- Atopy is common (allergy)
- Chronic, unrelenting rhinosinusitis
- Mass
 - May result in facial dysmorphism and proptosis
 - If proptosis is present, visual disturbances are reported
- Discharge
- Rhinorrhea
- Headache

Laboratory Tests

- Peripheral eosinophilia
- Elevated fungal-specific IgE
 - May also have elevated levels of fungal-specific IgG3
- Cultures performed to identify etiologic fungal agent
 - Results used to conduct desensitization treatments
 - Cultures are **not** used to provide antibiotic sensitivities since there is no invasive fungal infection

Treatment

- Options, risks, complications
 - Usually requires combination of surgery and medical therapy to yield best long-term outcome
- Surgical approaches
 - Extensive debridement and complete evacuation of impacted mucin is mainstay of therapy
 - Polypectomy and marsupialization of involved sinuses at minimum
 - Procedures may be endoscopic
 - Functional endoscopic sinus surgery (FESS)
- Drugs
 - Allergic desensitization (immunotherapy)
 - Postoperative anti-inflammatory therapy
 - Oral corticosteroids usually yield best outcome
 - Postoperative azoles (specifically, itraconazole) may reduce recurrences
 - Medical management of allergic inflammatory disease

Prognosis

- Good with integrated medical and surgical approach
- Recurrences develop with fair frequency
 - Can be problematic to functional status of patient

IMAGING

CT Findings

- Expansile, sometimes destructive mass within nasal cavity and paranasal sinuses
- Bone remodeling or destruction
 - Orbital expansion and bony erosion are prominent features
- Bone erosion can be seen in advanced cases

MACROSCOPIC

General Features

- Foul odor
- Polypoid fragments
- Putty or crunchy peanut butter-like consistency
- Muddy consistency
- Greasy to palpation

Size

- Range: 0.1-0.4 cm fragments of tissue
 - Mean overall aggregate: Up to 8 cm

MICROSCOPIC

Histologic Features

- Multiple polypoid fragments identified histologically
- "Mucinous" material is free floating, unattached to surrounding respiratory tissues
- "Tide lines," "tree rings," waves, or ripples
 - Appearance due to mucin material alternating with inflammatory debris
 - Yields overall "blue and pink" alternating appearance
- Degenerated material composed of neutrophils, eosinophils, and mucinous debris
 - Ghost outlines of cells common
 - Nuclear debris tends to aggregate
- Charcot-Leyden crystals (degenerated eosinophils)
 - Long, needle-shaped, or bipyramidal crystals
 - Dropped sub-stage condenser will yield refractile appearance to crystals
- Fungal elements are often difficult to detect (even with special stains)
 - Do not need to prove fungal elements are present (i.e., no need to do fungal stains)
 - When fungal elements not identified, EMRS can be used instead
- Concurrent sinonasal pathology
 - Sinonasal inflammatory polyps
 - Polyps may show inflammation but not abscesses or necrotic material
 - Chronic rhinosinusitis
 - Respiratory epithelial adenomatoid hamartoma

ANCILLARY TESTS

Histochemistry

- PAS-D
 - Highlights fungal hyphae (when present)
- Gomori methenamine silver (GMS)
 - May be difficult to interpret due to debris
 - Highlights fungal hyphae (when present)

DIFFERENTIAL DIAGNOSIS

Invasive Fungal Sinusitis

- Fungal hyphae identified
 - Within vessel walls or vascular spaces within tissue
- Significant host response within stroma
 - Inflammatory cells are identified within tissue rather than floating in lumen mucin as seen with AFS

Sinonasal Polyps

- Polypoid structures with intact surface epithelium
- Mucinous or edema material in background mixed with inflammatory cells
 - Eosinophils may be seen but usually not degenerated or associated with Charcot Leyden crystals
- Lacks alternating pattern
- Generally contains minor mucoserous glands in stroma

Mycetoma

- Aggregation or ball of fungi (yeasts &/or hyphae)
- Fruiting heads are common in this fungal disease
- Usually no host response
 - If present, can be lymphohistiocytic or eosinophilic
- Dematiaceous fungi most common

DIAGNOSTIC CHECKLIST

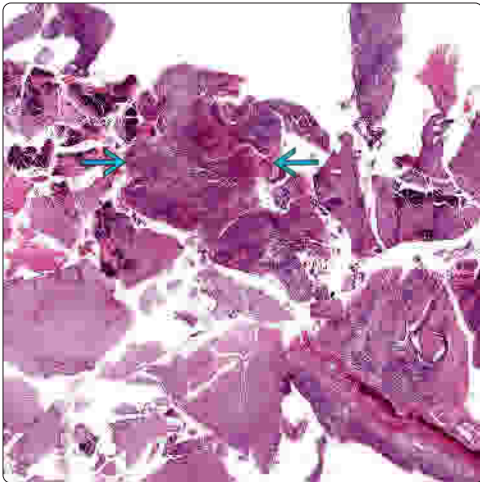
Pathologic Interpretation Pearls

- Alternating "tide lines" or "tree rings"
- Eosinophils and their breakdown products
- Do not need to prove fungal elements are present (i.e., no need to do fungal stains)

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AFS and Inflammatory Polyps



Degenerated Eosinophils and Mucin

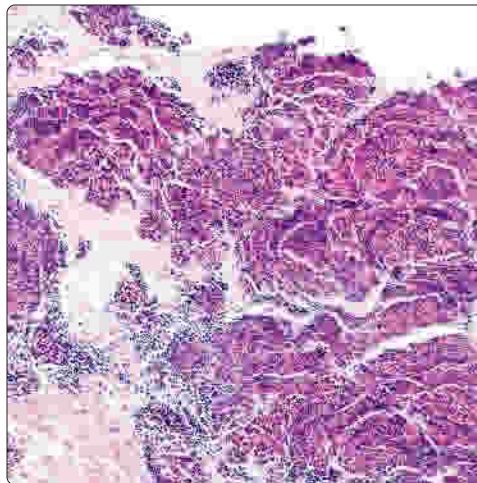


(Left) There is a background of sinonasal inflammatory polyps, with small collections of "allergic mucin" (seen between [arrows](#)). (Right) There is a tide line/tree ring type of alternating degenerated inflammatory cells with mucin.

Blue and Pink "Tide Lines" Are Classic

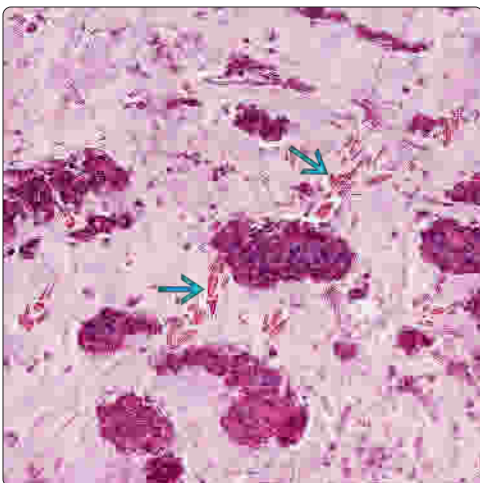


Debris of Eosinophils and Nuclear Debris

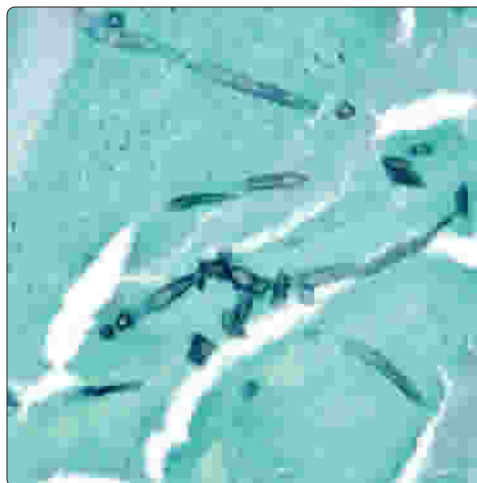


(Left) Hematoxylin & eosin shows alternating ripples of eosinophils and neutrophils. The mucinous to myxoid degeneration creates these "light" and "dark" rings or bands. This feature alone is quite characteristic of the disorder, seldom requiring any additional studies or evaluation. (Right) Hematoxylin & eosin shows degenerated inflammatory cells with mucinous material and neutrophilic and eosinophilic debris. The cracking artifacts within the tissue highlight the tide-line appearance.

Charcot-Leyden Crystals



Aspergillus Fungal Hyphae



(Left) There are numerous Charcot-Leyden crystals [seen](#) in this sample of AFS. The degenerated eosinophils are clumped, but not forming rings or tide lines. There is significant mucin in the background. (Right) The fungal hyphae can be highlighted with a variety of fungal stains, here shown with GMS. However, a PAS-D is often easier to interpret without as much debris or background staining.

Mycetoma

KEY FACTS

TERMINOLOGY

- Sinus fungal ball, fungus ball, noninvasive fungal sinusitis, noninvasive sinus mycetoma, "snotoma"
- Aggregation of fungal elements in sinus lumen, eliciting limited response, but not invading sinonasal tract tissues

ETIOLOGY/PATHOGENESIS

- Commensal fungi in nose may be source
- *Aspergillus* species most common

CLINICAL ISSUES

- All ages affected
- Equal gender distribution
- Maxillary sinus is most commonly affected (~85%)
- Unilateral nasal discharge, nasal obstruction, chronic sinusitis, and stuffiness
- Fungal cultures are usually negative
- Complete surgical extraction by functional endoscopic sinus surgery (FESS) performed at sinus ostium

- Antifungal therapy is not indicated

- Excellent; rare recurrence/persistence (< 4%)

IMAGING

- Heterogeneous opacification, microcalcifications, sinus expansion, and bone erosion (lysis) within sinus(es) on computed tomography


MICROSCOPIC

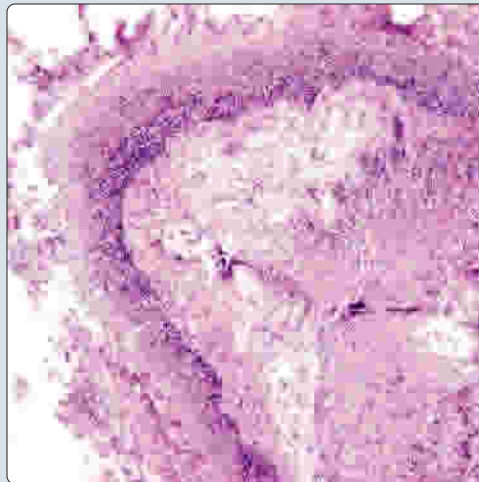
- Huge aggregates of hyphae, creating concretion or ball
- Identified within cavity spaces and not within mucosa or soft tissue

TOP DIFFERENTIAL DIAGNOSES

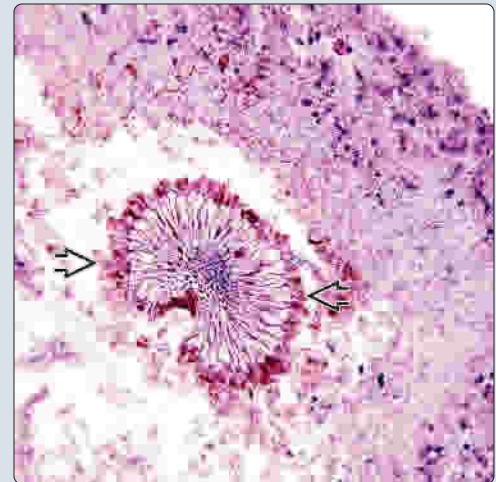
- Invasive fungal sinusitis
- Allergic fungal sinusitis
- Sinonasal inflammatory polyps

Mycetoma Fungal Elements


(Left) H&E shows myriad organisms aggregated to form a ball, with the yeast forming toward the periphery. There is no tissue involvement nor vascular invasion. (Right) H&E shows fungal organisms surrounding a fruiting head , a finding that can be seen in mycetoma. The species is unknown, but fungal cultures can document the type of fungus.

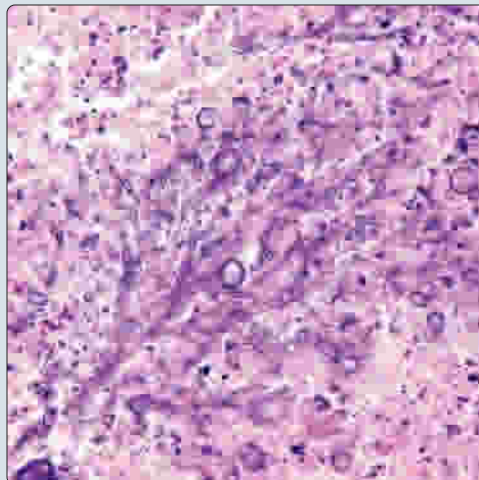


Fruiting Head

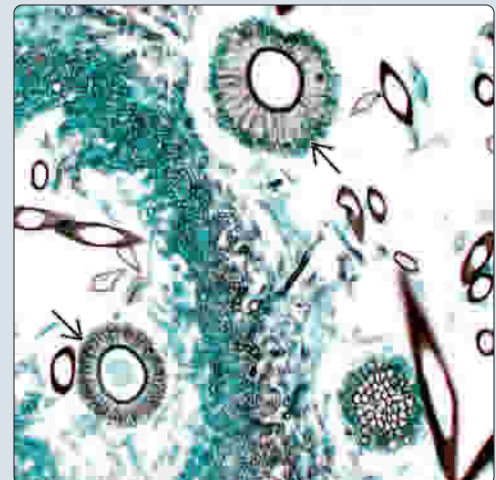


Aspergillus Organisms

(Left) H&E shows acute angle branching of hyphae, with yeast forms attached at the ends. This is an example of an aspergillus mycetoma. There is no tissue reaction. (Right) GMS highlights the fungal elements and fruiting heads , but is usually not required for diagnosis.



GMS Highlighting Fungal Organisms



KEY FACTS

TERMINOLOGY

- Chronic, progressive, granulomatous infection of upper airways caused by bacterium *Klebsiella rhinoscleromatis*

CLINICAL ISSUES

- Crowded conditions, poor hygiene, & nutrition contribute to transmission
- Endemic within Central America, Egypt, tropical Africa, India, Indonesia, Eastern Europe
- Peak in 2nd and 3rd decades
- Female > male
- Upper aerodigestive tract, nasal cavity specifically
- 3 overlapping clinical stages
 - Ozena (catarrhal phase): Includes atrophic rhinitis, with rhinorrhea
 - Granulomatous (proliferative phase): Granulomatous inflammation dominates and occludes nasal passages
 - Scleroma (cicatrical phase): Scarring and retraction of tissues

- Long-term antibiotic therapy and debridement

MICROSCOPIC

- Pseudoepitheliomatous hyperplasia, ulceration, and submucosal keratin cyst
- Sheets of inflammatory cells and histiocytes (Mikulicz cells)
 - Mikulicz cells are foamy histiocytes with organisms
- Dominant inflammatory cells are plasma cells including Mott cells and Russell bodies

ANCILLARY TESTS

- Warthin-Starry stain highlights encapsulated, nonmotile, rod-shaped bacilli in Mikulicz cells

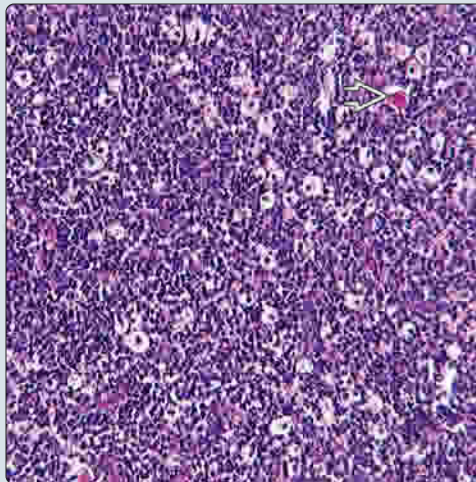
TOP DIFFERENTIAL DIAGNOSES

- Atypical mycobacteria
- Lepromatous leprosy
- Syphilis
- Rosai-Dorfman
- Wegener granulomatosis

Clinical Appearance of Rhinoscleroma

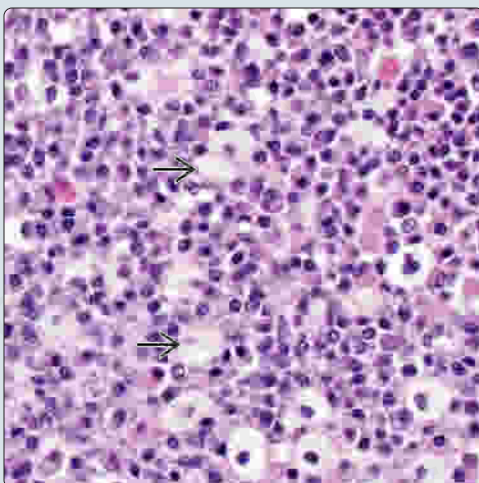


Lymphoid Cells With Histiocytes

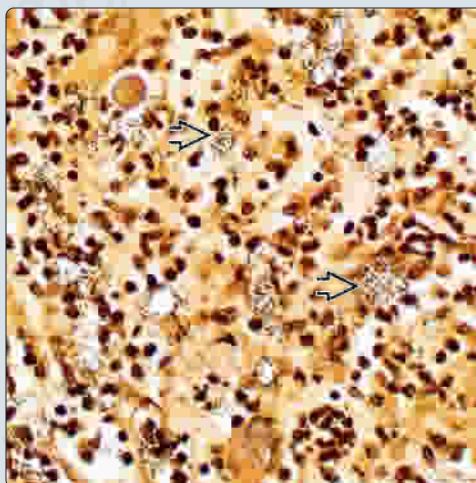


(Left) Clinical photograph shows nasal destruction in a 42-year-old man with a several year history of a progressively destructive lesion. A palatal perforation was also noted during intraoral exam. (Courtesy R. Carlos, DDS.) (Right) Hematoxylin & eosin (H&E) shows scattered histiocytes in a sea of lymphoid cells. These histiocytes are called Mikulicz cells after the physician who described the microscopic features of the disease. Note the Russell body.

Numerous Mikulicz Cells



Klebsiella Rhinoscleromatis Organisms



(Left) H&E shows multiple foamy macrophages (Mikulicz cells) within a background of lymphocytes. Organisms can often be seen on H&E. (Right) Warthin-Starry stain shows intracellular bacilli within the macrophages. Many times the cells will rupture and organisms will be seen in the background tissues. Other special stains do not reliably stain *Klebsiella rhinoscleromatis*.

KEY FACTS

TERMINOLOGY

- Acute, fulminant fungal infestation of sinonasal tract resulting in tissue destruction within days

CLINICAL ISSUES

- Clinical picture of fulminant infection more similar to clinical picture of mucormycosis than to clinical features of other forms of sinonasal aspergillosis
- Typical clinical scenario includes occurrence in immunocompromised patients (e.g., diabetics, immunosuppression)
- May occur in immunocompetent patients
- Requires surgical debridement with antifungal chemotherapy
- Mortality rates high
- Early diagnosis and treatment decreases morbidity and mortality

MICROSCOPIC

- Tissue necrosis is evident, but inflammatory response often is very limited
- Fungi seen within mucosal and submucosal tissues as well as in and around vascular spaces (angioinvasion)

ANCILLARY TESTS

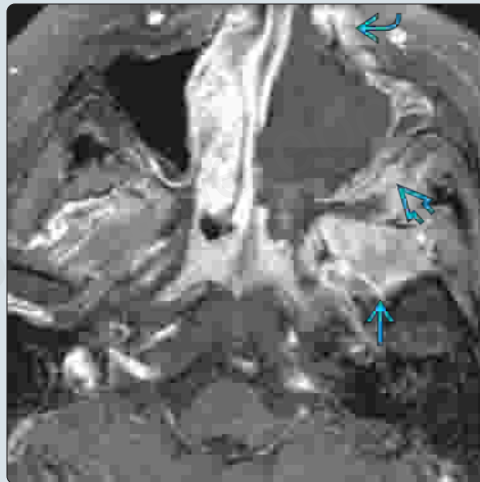
- Histochemical stains (GMS, PAS) positive
- In situ hybridization using specific fungal probes can effectively identify fungi in (acute) invasive fungal sinusitis as well as in species identification in specimens with negative cultures

TOP DIFFERENTIAL DIAGNOSES

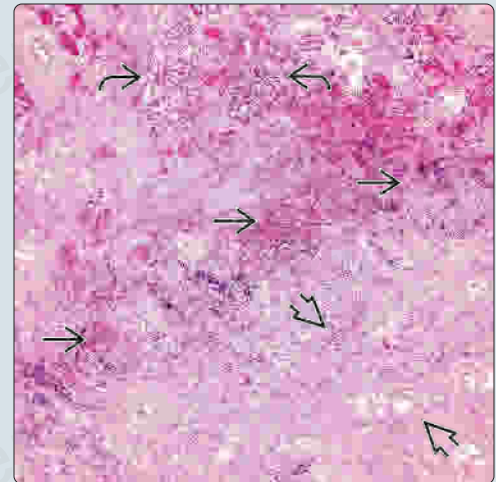
- In comparison to *Aspergillus*, *Mucor* hyphae are larger (7-20 μm), branch at haphazard angles (45-90°), and lack septations
- Granulomatosis with polyangiitis (Wegener granulomatosis)
- Hematolymphoid malignancy

MR: Invasive Fungal Sinusitis

(Left) Axial T1 C+ FS MR shows acute invasive left antral fungal sinusitis invading the pterygopalatine fossa and pterygomaxillary fissure, left premaxillary soft tissues, and masticator space. (Right) Resection material from invasive fungal sinusitis shows necrosis and infarction with effacement of the normal mucosal architecture, although residual seromucous glands are present.

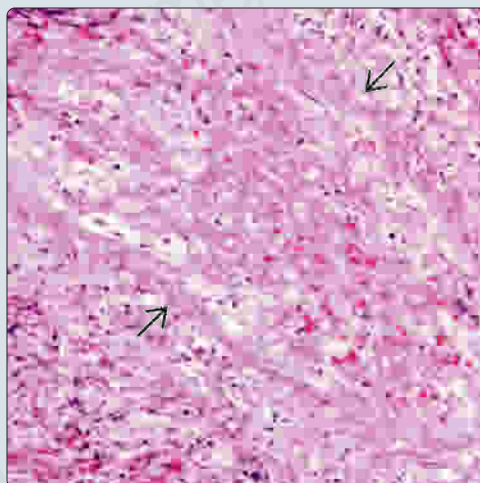


Invasive Fungal Sinusitis

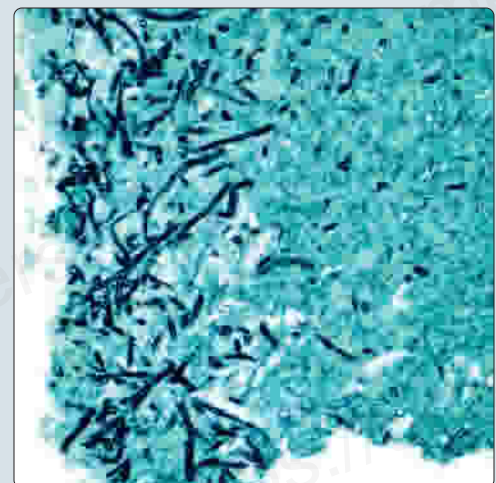


Vascular Thrombosis

(Left) H&E shows vascular thrombosis secondary to fungal invasion. The outlines of the organisms can be seen, although histochemical stains are required for definitive identification. The muscular wall assists in identifying the structure as a blood vessel. (Right) Necrotic material contain fungal spores and hyphae, the latter with septation and acute angle branching representing findings consistent with the *Aspergillus* species.



Aspergillus Species



TERMINOLOGY

Synonyms

- Acute fulminant *Aspergillus* sinusitis

Definitions

- Acute, fulminant fungal infestation of sinonasal tract often resulting in destruction of involved sinus(es) within days

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Most often caused by *Aspergillus* species
 - Other fungi found to be causative may include dematiaceous fungi
 - i.e., *Bipolaris*, *Exserohilum*, *Curvularia*, *Drechslera*, and *Alternaria*

CLINICAL ISSUES

Epidemiology

- Age
 - Most often occurs in adults but may occur in younger (immunocompromised) patients

Presentation

- Nasal discharge and sinus pain
 - Swelling of face (maxillary area and periorbital region) may be present
 - With progression of disease, blindness may occur
- Clinical picture of fulminant infection more similar to clinical picture of mucormycosis than to clinical features of other forms of sinonasal aspergillosis
- Typical clinical scenario includes occurrence in immunocompromised patients (e.g., diabetics, immunosuppression)
 - Immunosuppressed conditions may include post-transplant, malignant neoplasm
 - e.g., lymphoma
 - May occur in immunocompetent patients
- Patients may require immediate surgical debridement, often necessitating intraoperative consultation (i.e., frozen section) to determine cause of fulminant clinical picture
 - Pathologists tasked to histologically evaluate for presence of fungi
 - Intraoperative samples should be performed and sent for microbiologic cultures in order to speciate fungus

Treatment

- Options, risks, complications
 - Requires surgical debridement with antifungal chemotherapy, the latter include
 - Amphotericin B
 - Triazoles, including itraconazole, posaconazole, and voriconazole

Prognosis

- Mortality rates may be high with only 1/2 of patients surviving
- Early diagnosis and treatment decreases morbidity and mortality
- Diabetic patients appear to have better overall survival than patients with other comorbidities

- Patients who have intracranial involvement or who do not receive surgery as part of therapy have poor prognosis

MICROSCOPIC

Histologic Features

- Tissue necrosis is evident, but inflammatory response often is very limited
- Fungal forms are identified
 - *Aspergillus* hyphae are thin (2-5 µm) with acute angle branching (45°) and septated
 - Fungi seen within mucosal and submucosal tissues as well as in and around vascular spaces (angioinvasion)

ANCILLARY TESTS

Histochemistry

- Gomori methenamine silver (GMS)
 - Positive; delineates fungal forms
- Periodic acid-Schiff (PAS)
 - Positive; delineates fungal forms

In Situ Hybridization

- In situ hybridization using specific fungal probes can effectively identify fungi in (acute) invasive fungal sinusitis as well as in species identification in specimens with negative cultures

DIFFERENTIAL DIAGNOSIS

Mucormycosis

- In comparison to *Aspergillus*, *Mucor* hyphae are larger (7-20 µm), branch at haphazard angles (45-90°), and lack septations

Granulomatosis With Polyangiitis

- Formerly referred to as Wegener granulomatosis
- Absence of microorganisms and biocollagenolytic geographic-type ischemic-type necrosis
- Presence in active disease of elevated antineutrophil cytoplasmic autoantibodies &/or proteinase 3

Hematolymphoid Malignancy

- Characterized by malignant cellular infiltrate

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3. Montone KT et al: In situ hybridization for specific fungal organisms in acute invasive fungal rhinosinusitis. *Am J Clin Pathol*. 135(2):190-9, 2011
4. Kasapoglu F et al: Acute invasive fungal rhinosinusitis: evaluation of 26 patients treated with endonasal or open surgical procedures. *Otolaryngol Head Neck Surg*. 143(5):614-20, 2010
5. Nakaya K et al: New treatment for invasive fungal sinusitis: three cases of chronic invasive fungal sinusitis treated with surgery and voriconazole. *Auris Nasus Larynx*. 37(2):244-9, 2010
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8. Ghadiali MT et al: Frozen-section biopsy analysis for acute invasive fungal rhinosinusitis. *Otolaryngol Head Neck Surg*. 136(5):714-9, 2007
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KEY FACTS

TERMINOLOGY

- Chronic infectious disease of the upper respiratory tract characterized by formation of polypoid masses and caused by the sporulating organism *Rhinosporidium seeberi*

ETIOLOGY/PATHOGENESIS

- Transmission thought to occur via water or dust
- R. seeberi*
 - Fungal organism
 - Not considered contagious

CLINICAL ISSUES

- Endemic in India, Sri Lanka, and Brazil
 - Only sporadic occurrence in USA
- Most commonly involves nasal cavity and nasopharynx
- Infection may involve other mucosal sites
 - e.g., larynx, tracheobronchial tree, esophagus, pharynx, oral cavity, palpebral conjunctiva, ears
- Surgical excision

- Antibiotic therapy not effective
- Recurrences in up to 10% of cases

MICROSCOPIC

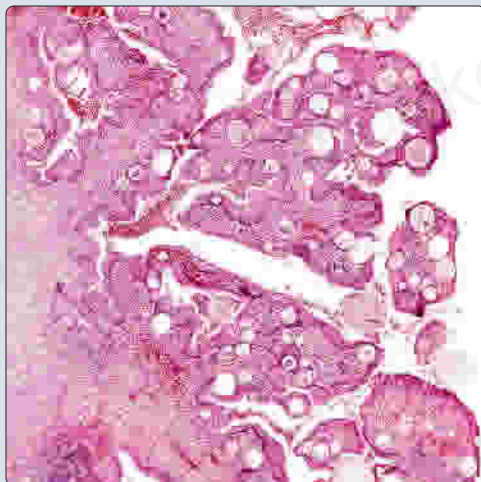
- Mucosal and submucosal cysts (sporangia) ranging in size from 10-300 μm in diameter
- Sporangia contain innumerable sporangiospores (endospores) seen by hematoxylin and eosin
- Microorganisms stain with mucicarmine and PAS
- Rupture of cysts will induce acute inflammatory response

TOP DIFFERENTIAL DIAGNOSES

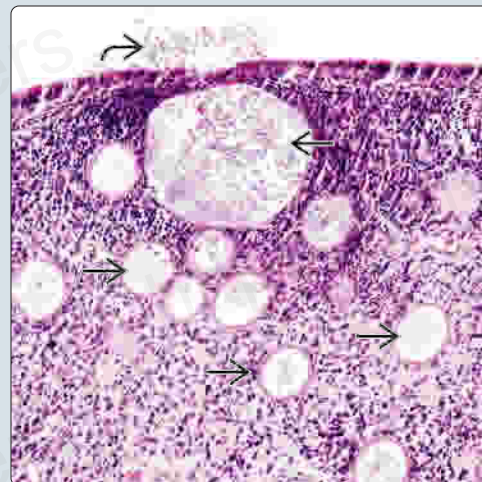
- Coccidiomycosis
 - Coccidioides immitis* does not stain with mucin
 - R. seeberi* is usually much larger than *C. immitis*
- Schneiderian papilloma, cylindrical cell type
 - Cysts associated with schneiderian papilloma only intraepithelial

Polypoid Lesion

(Left) This polypoid proliferation is characterized by the presence of intraepithelial and submucosal cysts (sporangia). There is squamous metaplasia and irregular hyperplasia of the surface epithelium. (Right) Thick-walled submucosal cysts (sporangia) of variable sizes contain endospores of varying maturation. One of the cysts ruptured with extrusion of endospores through the surface epithelium.

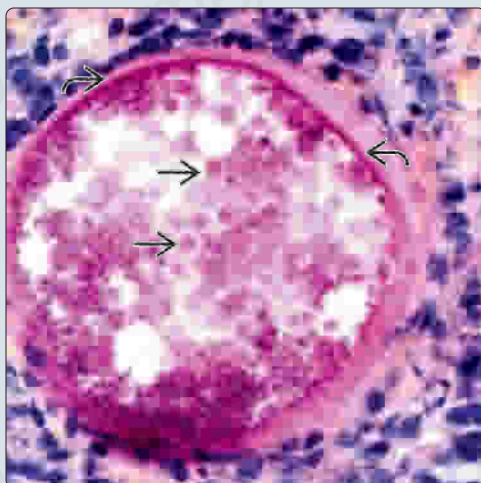


Submucosal Cysts

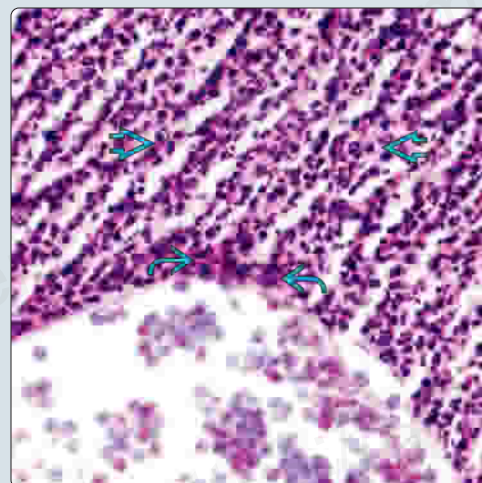


Cyst With Endospores

(Left) The endospores are mucicarmine positive. The thick wall of the sporangium is also mucicarmine positive. (Right) Rupture of this cyst resulted in microabscess formation characterized by a sea of neutrophils. Endospores are visible outside the cyst wall. Granulomatous reaction is usually not seen, but cyst rupture may result in presence of multinucleated giant cells (not shown).



Ruptured Cyst With Abscess Formation



TERMINOLOGY

Definitions

- Chronic infectious disease of upper respiratory tract characterized by formation of polypoid masses and caused by the sporulating organism *Rhinosporidium seeberi*

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Thought to be zoonotic as rhinosporidiosis seen in cattle, horses, and mules
- Transmission thought to occur via water or dust
 - Endospore penetrates nasal mucosa and matures into sporangium in submucosal compartment
 - Following maturation, sporangia burst releasing endospores into surrounding tissue

Infectious Agents

- R. seeberi*
 - Fungal organism
 - Does not grow on synthetic media
 - Has been propagated in cell culture media
 - Not considered contagious

CLINICAL ISSUES

Epidemiology

- Incidence
 - Endemic in India, Sri Lanka, and Brazil
 - Only sporadic occurrence in USA
- Age
 - All ages but common in 3rd and 4th decades
- Sex
 - Male > female

Site

- Most commonly involves nasal cavity (inferior turbinate along lateral nasal wall) and nasopharynx
 - Infection may involve other mucosal sites
 - e.g., larynx, tracheobronchial tree, esophagus, pharynx, oral cavity, palpebral conjunctiva, ears

Presentation

- Patients are usually healthy
- Symptoms include
 - Nasal obstruction, epistaxis, rhinorrhea

Treatment

- Surgical approaches
 - Surgical excision
- Drugs
 - Antibiotic therapy not effective

Prognosis

- Recurrences necessitating additional surgical excision may occur in up to 10% of cases

MACROSCOPIC

General Features

- Single or multiple polypoid, pedunculated, or sessile masses

MICROSCOPIC

Histologic Features

- Mucosal and submucosal cysts (sporangia) ranging in size from 10-300 μ m in diameter
- Sporangia contain innumerable sporangiospores (endospores) seen by hematoxylin and eosin
 - 2 sizes of sporangiospores may be seen
 - Smaller spores measuring ~ 1-2 μ m in diameter
 - Larger spores measuring ~ 5-10 μ m in diameter
 - Larger spores are more mature forms
 - Tend to congregate toward the center with smaller being more peripheral, creating zonated appearance relative to spore size
- Smaller cystic structures (without sporangiospores) ranging from 10-100 μ m are also seen
 - Called trophocysts
 - Considered to result from autoinfection via mature sporangiospores released from sporangia
 - Sporangia and trophocysts have eosinophilic walls measuring several μ m in thickness
- Chronic inflammatory response consisting of lymphocytes, plasma cells, and eosinophils accompany microorganisms
- Rupture of cysts will induce acute inflammatory response
 - Granulomatous reaction usually not seen, but cyst rupture may result in presence of multinucleated giant cells
- Overlying epithelium may be hyperplastic &/or demonstrate squamous metaplasia

ANCILLARY TESTS

Histochemistry

- PAS and mucicarmine
 - Reactivity: Positive

DIFFERENTIAL DIAGNOSIS

Coccidiomycosis Infection

- R. seeberi* is usually much larger than *Coccidioides immitis*
- C. immitis* does not stain with mucicarmine
 - Wall of *R. seeberi* stains with mucicarmine

Schneiderian Papilloma, Cylindrical Cell Type

- Cysts associated with schneiderian papilloma only intraepithelial
 - Cysts of rhinosporidiosis intraepithelial and submucosal

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- Thianprasit M et al: Rhinosporidiosis. *Curr Top Med Mycol.* 3:64-85, 1989
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Mycobacterium leprae Infection

KEY FACTS

TERMINOLOGY

- Infection caused by *M. leprae* characterized by cutaneous, mucosal, peripheral nerve involvement

ETIOLOGY/PATHOGENESIS

- Host genetic factors are thought to influence susceptibility to infection as well as disease progression
 - Variants of genes in NOD2-mediated signaling pathway (regulates innate immune response) are associated with susceptibility to infection with *M. leprae*

CLINICAL ISSUES

- Peripheral nerve involvement results in pain and sensory loss
- Sinonasal tract involvement important in transmission of disease as numerous bacilli in nasal secretions
- 2 main clinical presentations occur based on immune reaction to the microorganism include lepromatous and tuberculoid leprosy

- Antibiotic therapy

- Rifampin and dapsone for tuberculoid leprosy
- Rifampin and dapsone and clofazimine for lepromatous leprosy

MICROSCOPIC

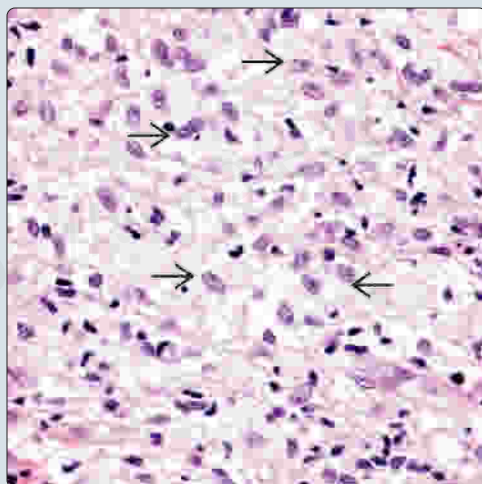
- **Lepromatous leprosy**
 - Presence of sheets of lymphocytes and vacuolated histiocytes (lepra cells)
- **Tuberculoid leprosy (paucicellular leprosy)**
 - Noncaseating granulomatous inflammation

ANCILLARY TESTS

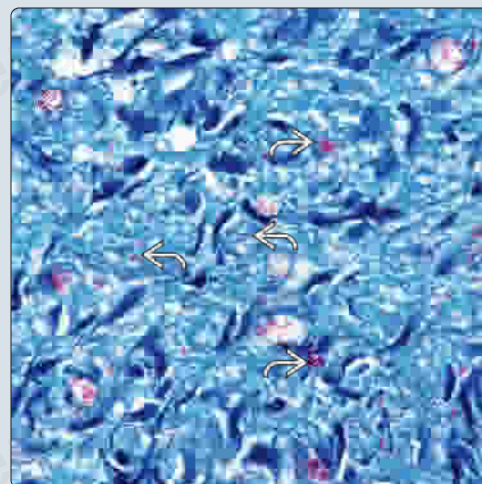
- Fite stain (modified acid-fast bacilli stain)
 - Abundant organisms in lepromatous leprosy
 - Scarce to absent organisms in tuberculoid leprosy
- Rapid quantitative serological test assists in detection of *M. leprae* infection

Lepra Cells in Lepromatous Leprosy

(Left) Lepromatous leprosy shows a diffuse proliferation of vacuolated histiocytes (so-called lepra cells) [1]. In contrast to tuberculoid leprosy, well-formed granulomas are not present. (Right) Abundant red-staining *Mycobacterium leprae* microorganisms, in clusters and as individual organisms [2], are present within the vacuolated histiocytes (lepra cells).

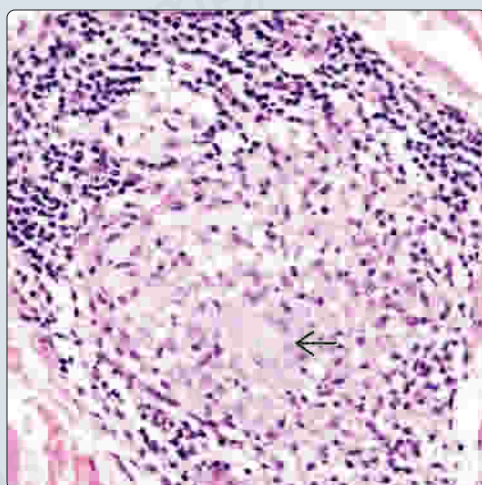


***M. Leprae* Microorganisms**

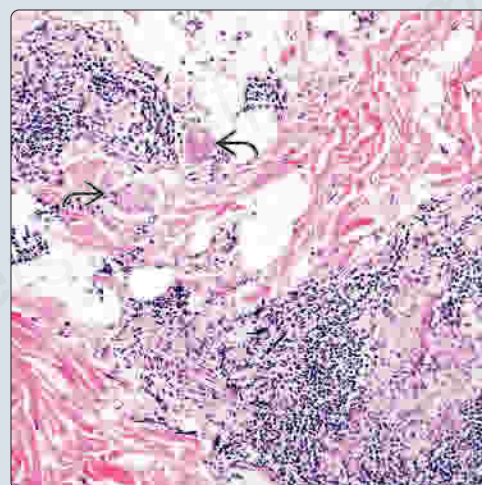


Granuloma in Tuberculoid Leprosy

(Left) Tuberculoid leprosy shows well-formed noncaseating granulomas of epithelioid histiocytes and multinucleated giant cells [3]. Microorganisms were sparse to absent by histochemical staining. Molecular analysis (e.g., in situ hybridization) could assist in identifying the causative microorganism. (Right) Granulomas of tuberculoid leprosy approximate small peripheral nerves [4]; the latter were S100 protein positive (not shown).



Approximation to Peripheral Nerves



TERMINOLOGY

Synonyms

- Hansen disease

Definitions

- Infection caused by *Mycobacterium leprae* characterized by cutaneous, mucosal, and peripheral nerve involvement

ETIOLOGY/PATHOGENESIS

Infectious Agents

- *M. leprae*
 - Low infectivity and exposure rarely results in infection
 - Believed to require cool host body temperature for survival
 - Affects cooler peripheral areas of body, including digits, ears, nose, nasal cavity
- Sinonasal tract (mucosal) involvement fairly common and may be important in transmission of disease
 - Nasal secretions contain high numbers of bacilli
 - Initial site of infection may be nasal or oropharyngeal mucosa
 - Oral lesions are not uncommon
- Host genetic factors are thought to influence susceptibility to infection as well as disease progression
 - Variants of genes in NOD2-mediated signaling pathway (regulates innate immune response) are associated with susceptibility to infection with *M. leprae*

CLINICAL ISSUES

Site

- Patients with sinonasal tract involvement may present with
 - Mucopurulent rhinosinusitis, nosebleeds, and anosmia
 - Early lesions may appear plaque-like
 - Late lesions may be ulcerative and nodular and may result in collapse of bridge of nose
 - Due to involvement of peripheral nerves, pain and muscular atrophy as well as sensory loss occur frequently

Presentation

- 2 main clinical presentations occur based on immune reaction to microorganism
 - **Lepromatous leprosy**
 - Also referred to as multibacillary leprosy
 - Develops in patients with reduced cell-mediated immune reaction
 - Disease is usually diffuse
 - Face is common site of involvement that may result in so-called "leonine facies" due to skin enlargement and facial distortion
 - Lepromin skin test is negative
 - Microorganisms are typically present in skin biopsy
 - **Tuberculoid leprosy**
 - Also referred to as paucibacillary leprosy
 - Develops in patients with high immune reaction
 - Disease is usually localized
 - Lepromin skin test is positive
 - Microorganisms are typically absent in skin biopsy

Treatment

- Drugs
 - Antibiotic therapy
 - Rifampin and dapsone for tuberculoid leprosy (6 month course)
 - Rifampin and dapsone and clofazimine for lepromatous leprosy (12 month course)

MICROSCOPIC

Histologic Features

- 2 types of histopathologic processes can be seen
 - **Lepromatous leprosy**
 - Absence of granulomatous inflammation
 - Presence of sheets of lymphocytes and vacuolated histiocytes (lepra cells)
 - Abundant microorganisms by special stains
 - **Tuberculoid leprosy**
 - Well-formed granulomatous inflammation with admixture of histiocytes, multinucleated giant cells, and lymphocytes
 - Paucity of microorganisms by special stains
 - May approximate or surround peripheral nerves
 - **For both types**
 - Histopathologic process typically located in submucosa with intact surface epithelium
 - Pseudoepitheliomatous hyperplasia may be present

ANCILLARY TESTS

Histochemistry

- Fite stain (modified acid-fast bacilli stain)
 - Positive
 - Abundant organisms in lepromatous leprosy
 - Scarce to absent organisms in tuberculoid leprosy

In Situ Hybridization

- Rapid quantitative serological test assists in detection of *M. leprae* infection
 - New leprosy serological test (NDO-LID) detects larger proportions of leprosy infection than alternative Standard Diagnostics leprosy test including detection of paucibacillary leprosy

DIFFERENTIAL DIAGNOSIS

Mycobacterium tuberculosis

- Characterized by caseating granulomatous inflammation
- Acid-fast bacilli may be identified by special stains

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KEY FACTS

TERMINOLOGY

- Nonspecific or specific inflammation of sinonasal tract

ETIOLOGY/PATHOGENESIS

- Allergic rhinosinusitis
 - Most common cause in adults and 2nd most common cause (to viruses) in children
- Infectious rhinosinusitis
 - Caused by variety of microorganisms; most common include viruses and bacteria
- Atrophic rhinosinusitis
 - Caused by variety of factors, including chronic bacterial infection, nutritional deficiencies, chronic exposure to irritants, prior radiation or surgery, end stage of chronic infections, autoimmune disease
- Aspirin intolerance
 - Referred to as Samter triad or syndrome: Includes aspirin intolerance, sinonasal polyps, asthma

CLINICAL ISSUES

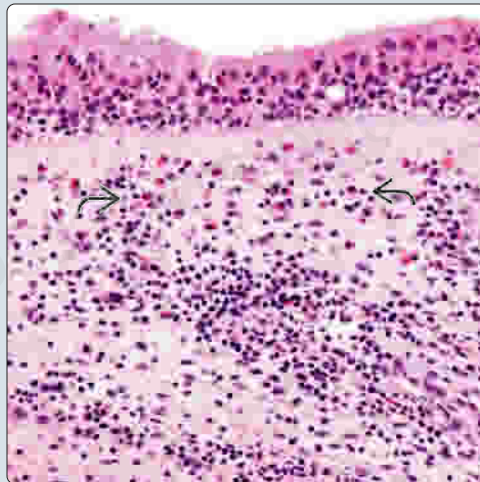
- For all types of rhinosinusitis
 - Prognosis excellent with cure following appropriate therapy
 - Self-limiting disease
 - Atrophic rhinosinusitis may spontaneously arrest
- Surgery (e.g., functional endoscopic sinus surgery) may be used in atrophic rhinosinusitis and aspirin intolerance, latter for removal of polyps

MICROSCOPIC

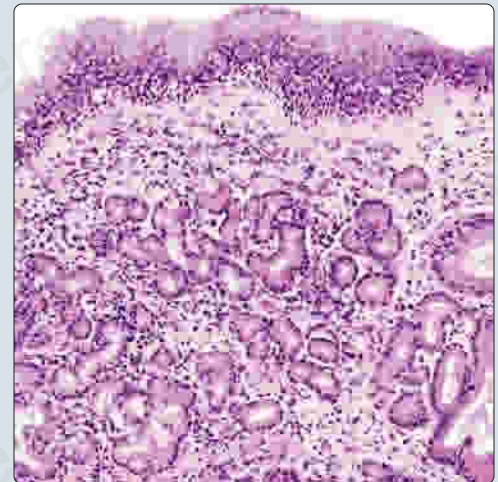
- Submucosal mixed inflammatory cell infiltrate, including mature lymphocytes with variable admixture of plasma cells, eosinophils, histiocytes, and neutrophils
- Epithelial hyperplasia with papillary appearance (hyperplastic papillary sinusitis) may be present in long-standing, recurrent or persistent disease

Allergic Rhinosinusitis

(Left) Chronic allergic rhinosinusitis shows submucosal edematous change and associated mixed inflammatory cell infiltrate, including numerous eosinophils. (Right) Nonspecific chronic sinusitis includes a mixed inflammatory cell infiltrate, including lymphocytes, plasma cells, and eosinophils with intact respiratory epithelium and seromucous glands.

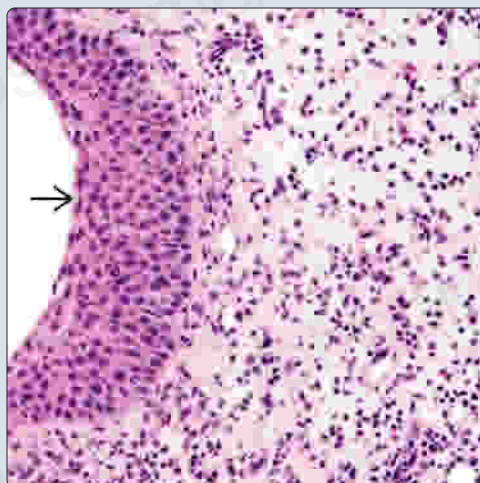


Nonspecific Chronic Rhinosinusitis

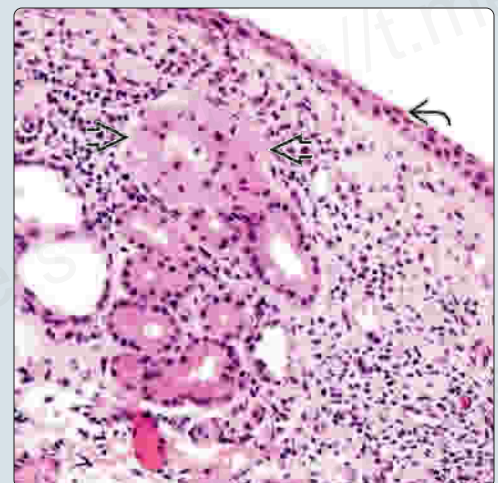


Nonspecific Chronic Rhinosinusitis

(Left) Submucosal edematous stroma with admixture of acute and chronic inflammatory cells including mild increase in eosinophils is shown. Surface squamous metaplasia is present. (Right) Squamous metaplasia of the surface respiratory epithelium can be seen in all types of sinusitis. Although uncommon in association with (chronic) sinusitis, oncocyctic metaplasia of seromucous glands may be seen.



Squamous Metaplasia



TERMINOLOGY**Definitions**

- Nonspecific or specific inflammation of sinonasal tract
 - May be isolated to nasal cavity (rhinitis)
 - Isolated to paranasal sinuses (sinusitis)
 - Involves both nasal cavity and paranasal sinuses (rhinosinusitis)

ETIOLOGY/PATHOGENESIS**Developmental Anomaly**

- Structural or mechanical causes include
 - Deviated nasal septum, neoplasms, primary ciliary dyskinesia

Environmental Exposure

- **Allergic rhinosinusitis**
 - In adults, allergies most common cause
 - In children, viral upper respiratory infection most common cause followed by allergies

Infectious Agents

- **Infectious rhinosinusitis**
 - Caused by variety of microorganisms; most common are viruses and bacteria
 - Viral rhinosinusitis results in common cold
 - Common viruses implicated include rhinoviruses, influenza and parainfluenza viruses, adenoviruses, respiratory syncytial virus
 - Bacterial sinusitis
 - More common bacteria implicated include *Streptococcus pneumoniae*, *Haemophilus influenzae*, α -hemolytic streptococci

Other Causes

- Atrophic rhinosinusitis
 - Also referred to as ozena (stench) and rhinitis sicca
 - Caused by variety of factors, including the following
 - Chronic bacterial infection, nutritional deficiencies (e.g., vitamin A, iron)
 - Chronic exposure to irritants
 - Prior radiation or surgery
 - End stage of chronic infections
 - Hypoestrogenemia
 - Autoimmune disease
- Aspirin intolerance or aspirin-exacerbated respiratory disease
 - Also referred as Samter triad or syndrome: Includes aspirin intolerance, sinonasal polyps (usually bilateral), asthma
- Nonallergic rhinosinusitis with eosinophilia syndrome
 - May be precursor to aspirin intolerance syndrome
- Idiopathic
- Occupational or environmental exposure
- Systemic diseases
 - Cystic fibrosis, others
- Medication induced
 - Referred to as rhinosinusitis medicamentosa
 - May be caused by topical or systemic medications (e.g., propranolol, oral contraceptives, reserpine), nasal sprays
- Pregnancy

- Thought to result from combined effects on nasal mucosa by pregnancy-related hormones, increased blood volume, and airway resistance

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Estimated 1 billion colds in USA annually
- Age
 - **Allergic, infectious, and nonspecific rhinosinusitis**
 - Occurs over wide age range from very young to very old
 - **Atrophic rhinosinusitis**
 - Begins in childhood often in 2nd decade of life at onset of puberty
 - **Aspirin intolerance**
 - Often begins in 3rd-4th decades of life

Presentation

- **Allergic rhinosinusitis**
 - In sensitized patient, exposure results in allergic reaction, producing nasal congestion with rhinorrhea, sneezing, itching
 - Reaction begins within minutes of exposure, peaking ~ 15 minutes later
- **Infectious rhinosinusitis**
 - Associated with pain localized over infected site, headaches are uncommon
 - Acute symptoms
 - Persistent and worsening symptoms longer than 7 days but less than 3 weeks
 - Subacute symptoms
 - 3 weeks-3 months
 - Chronic symptoms
 - Lasting more than 3 months
 - Patients with resistant or refractory chronic sinusitis have increased incidence of *Streptococcus aureus*, anaerobic bacteria, gram-negative organisms
 - *Pseudomonas aeruginosa* commonly cultured organism in patients receiving multiple courses of antibiotics over extended periods
- **Atrophic rhinosinusitis**
 - Symptoms include nasal obstruction, headaches, nasal crusting, anosmia, epistaxis, halitosis, and foul-smelling nasal odor
- **Aspirin intolerance**
 - Within hours of aspirin ingestion, patients may experience bronchoconstriction and rhinorrhea
 - In some patients, may also follow ingestion of nonsteroidal anti-inflammatory medications
 - Symptoms may include nausea, vomiting, diarrhea with gastrointestinal cramping
 - Felt to be pharmacologic with interference in metabolism of arachidonic acid rather than allergic response

Endoscopic Findings

- **Allergic and nonspecific rhinosinusitis**
 - Sinonasal mucosa is pale to bluish
 - Inflammatory polyps may or may not be identified
- **Atrophic rhinosinusitis**

- Characterized by atrophy of nasal mucosa, crust formation, and foul-smelling odor from nasal cavity
- **Aspirin intolerance**
 - Polyps can be identified and are usually bilateral
 - More severe symptoms with less improvement after surgery with significantly higher need for revision surgery

Laboratory Tests

- **Allergic rhinosinusitis**
 - Gold standard for allergy testing is considered skin testing
- **Infectious rhinosinusitis**
 - Microbiologic culturing for viral (e.g., H1N1) and bacterial pathogens
 - Drug sensitivity testing for bacterial infection

Treatment

- Surgical approaches
 - Surgery (e.g., functional endoscopic sinus surgery) may be used in atrophic rhinosinusitis and aspirin intolerance, latter for removal of polyps
- Drugs
 - **Allergic rhinosinusitis**
 - Antihistamines
 - Immunotherapy for documented IgE-mediated allergies
 - **Infectious rhinosinusitis**
 - Antibiotic therapy indicated for bacterial infection
 - **Atrophic rhinosinusitis**
 - Antibiotics and nutritional supplements (e.g., vitamin A, iron, estrogen)
 - **Aspirin intolerance**
 - Avoidance of instigating medications
 - Symptomatic relief
 - **Nonspecific rhinosinusitis**
 - Symptomatic relief

Prognosis

- For all types of rhinosinusitis, prognosis is excellent with cure following appropriate therapy

IMAGING

Radiographic Findings

- **Acute rhinosinusitis**
 - Air-fluid levels represent best diagnostic clue
- **Chronic rhinosinusitis**
 - Mucosal thickening or soft tissue opacification of nonexpanded sinus with thickening and sclerosis of sinus bony walls

MICROSCOPIC

Histologic Features

- **Allergic rhinosinusitis**
 - Submucosal edema with mixed inflammatory cell reaction dominated by presence of eosinophils
 - Neutrophils can be identified, especially in presence of secondary bacterial infection
 - Squamous metaplasia of surface epithelium may be present

- **Atrophic rhinosinusitis**
 - Squamous metaplasia of surface epithelium
 - Submucosal edema with nonspecific chronic inflammation, fibrosis
 - Atrophic changes of seromucous glands
- **Aspirin intolerance**
 - Polyps histologically similar to sinonasal inflammatory polyps not occurring in aspirin-intolerant patients
- **Nonspecific chronic sinusitis**
 - Submucosal mixed inflammatory cell infiltrate, including mature lymphocytes with variable admixture of plasma cells, eosinophils, histiocytes, and neutrophils
 - Benign lymphoid aggregates may be present
 - Submucosal edematous change
 - Surface mucosa squamous metaplasia often (but not uniformly) present
- In longstanding &/or recurrent/persistent disease, changes may include
 - Epithelial hyperplasia with papillary appearance (hyperplastic papillary sinusitis)

DIFFERENTIAL DIAGNOSIS

Adenocarcinoma

- Complex architectural growth patterns (e.g., back-to-back glands) composed of single-cell type

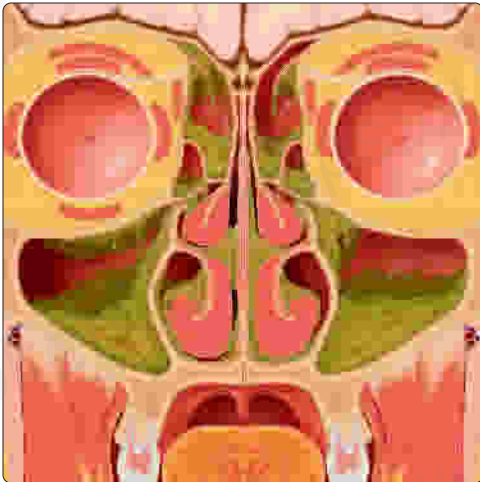
Schneiderian Papilloma

- Presence of thickened squamoid appearing epithelium with endophytic or exophytic growth and associated mucocytes, microcysts, and inflammatory cells

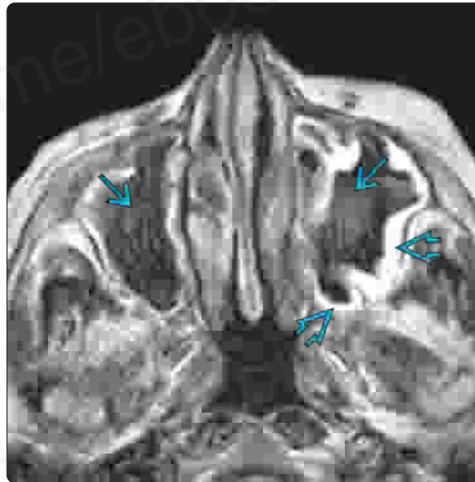
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Sinusitis

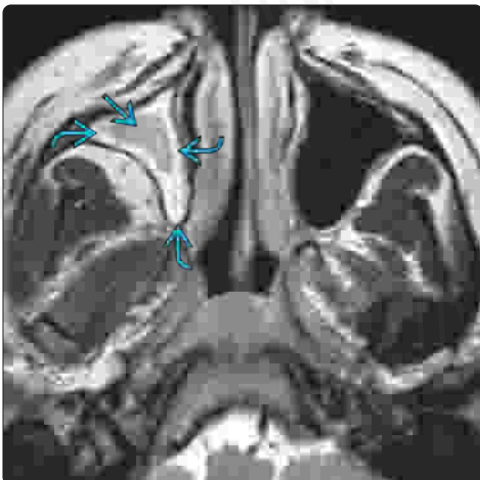


Chronic Rhinosinusitis

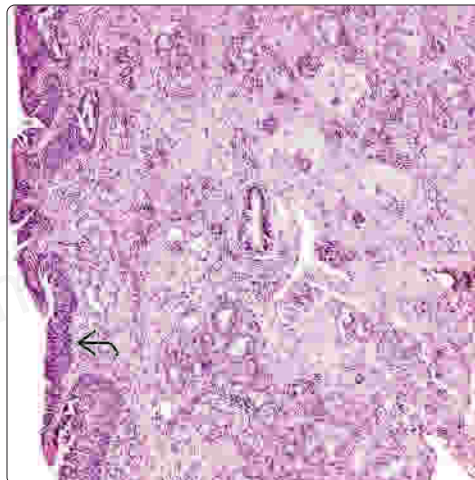


(Left) Mucus accumulation in sinusitis results in variable accumulation with the nasal cavity and paranasal sinuses, which in turn results in clinical symptoms, including congestion, anosmia, and radiologic evidence of air-fluid levels and opacification. (Right) Axial T2WI MR reveals low signal in the proteinaceous, inspissated secretions [] opacifying both maxillary sinuses. Hyperintense inflamed mucosa is noted at the periphery of the left maxillary sinus [].

Chronic Rhinosinusitis



Atrophic Rhinitis

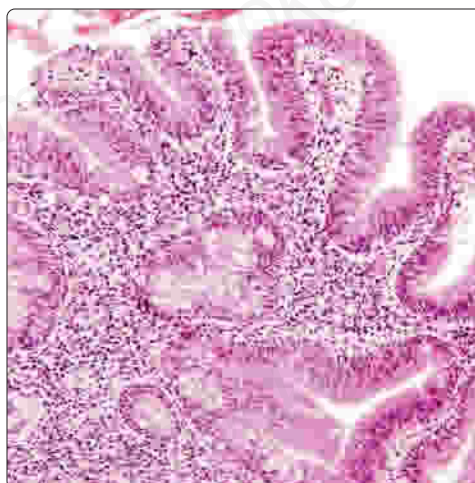


(Left) Axial T2 MR demonstrates an opacified, nonexpanded right maxillary sinus. The central secretions within the sinus are heterogeneous with low signal [], surrounded by hyperintense peripheral inflamed mucosa []. (Right) Atrophic rhinitis includes squamous metaplasia of surface epithelium [], atrophy of seromucous glands, nonspecific chronic inflammation, submucosal fibrosis, and submucosal edematous change.

Chronic Rhinosinusitis



Papillary Sinusitis



(Left) Tangentially sectioned epithelium with thickened appearance and downward (inverted) pattern may suggest a diagnosis of a schneiderian papilloma, inverted type. (Right) In longstanding &/or recurrent/persistent disease, changes may include epithelial hyperplasia with papillary appearance referred to as hyperplastic papillary sinusitis.

Granulomatosis With Polyangiitis

KEY FACTS

TERMINOLOGY

- Nonneoplastic, idiopathic aseptic necrotizing disease with predilection for upper/lower respiratory tract and genitourinary system characterized by vasculitis and destructive properties

CLINICAL ISSUES

- In upper aerodigestive tract, most common site of occurrence is sinonasal region with nasal cavity > maxillary > ethmoid > frontal > sphenoid
- Symptoms vary according to site of involvement, including
 - Sinonasal tract: Sinusitis ± purulent rhinorrhea, obstruction, pain, epistaxis, anosmia, headaches
- Important adjunct evaluation includes
 - Elevated antineutrophil cytoplasmic antibody (ANCA)
 - Reported specificity for diagnosis of granulomatosis with polyangiitis (GPA) from 85-98%
 - GPA characteristically associated with c-ANCA and only infrequently with p-ANCA


- Elevated proteinase 3 (PR3)


- Most patients receive combination of cyclophosphamide and prednisone for remission induction
- Treatment with cyclophosphamide and prednisone results in 75% complete remission rate

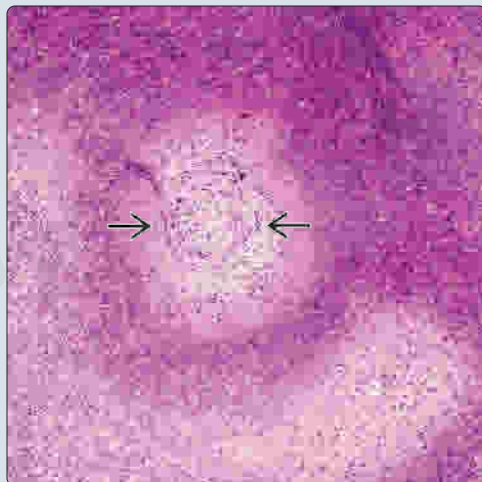
MICROSCOPIC

- Classic triad includes vasculitis, granulomatous inflammation, tissue necrosis
 - In practice, finding classic histologic triad in single biopsy or series of biopsies is very uncommon
- Inflammatory cell infiltrate angiocentric and angioinvasive
- Ischemic- or geographic-type (multifocal necrobiosis) with basophilic smudgy appearance
- Well-formed granulomas not typical feature
 - Characterized by scattered or isolated multinucleated giant cells

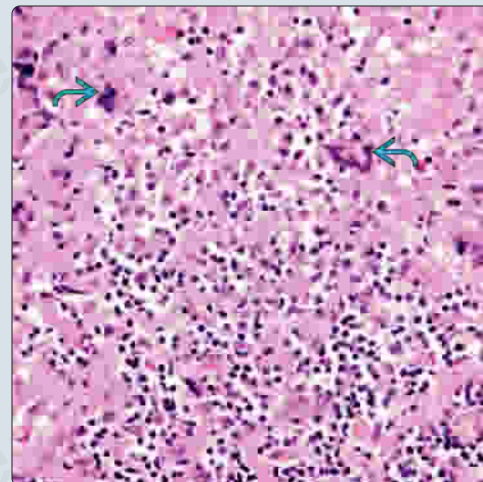
Vascular Thrombosis and Ischemic Necrosis

(Left) Ischemic-type necrosis with a basophilic smudgy appearance surrounds an ablated vascular space . The necrosis should be deep within the tissue and not limited to the surface of the tissue.


(Right) A mixed chronic inflammatory cell infiltrate is present, lacking atypia or malignant features. Scattered multinucleated giant cells are seen , but well-formed granulomas are not identified. The presence of well-formed granulomas should prompt consideration for alternative diagnoses (e.g., infectious disease, sarcoidosis).




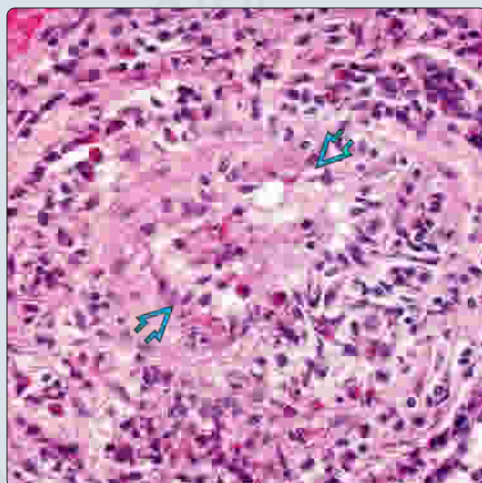
Multinucleated Giant Cells



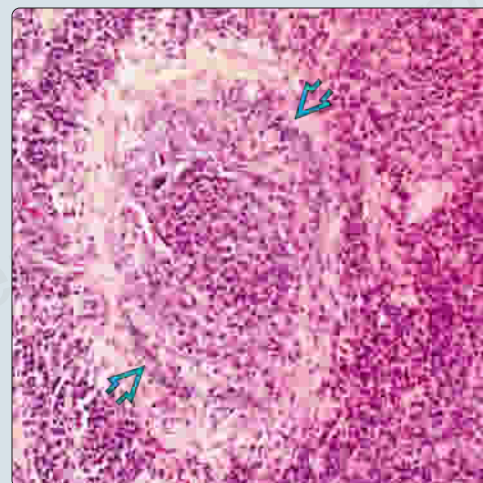
Vasculitis

(Left) Vasculitis includes inflammatory infiltrate concentrically surrounding a blood vessel (angiocentric) with (or without) invasion through the vessel wall (angioinvasion), resulting in near occlusion of the endothelial-lined lumen .

(Right) Elastic stain shows disruption of the black staining external elastic membrane  by the angiocentric and angioinvasive inflammatory cell infiltrate. The inflammatory infiltrate completely obliterates the vessel lumen.



Vasculitis



TERMINOLOGY

Abbreviations

- Granulomatosis with polyangiitis (GPA)
- Upper aerodigestive tract (UADT)

Synonyms

- Formerly referred to as Wegener granulomatosis (WG)

Definitions

- Nonneoplastic, idiopathic aseptic necrotizing disease with predilection for upper/lower respiratory tract and genitourinary system characterized by vasculitis and destructive properties
 - Classic definition calls for involvement of head and neck region, lungs, and kidney
 - Majority of patients do not exhibit classic clinical triad simultaneously at time of initial presentation
 - Possible that initial biopsy material may originate from lesions of UADT in absence of clinical suspicion for GPA

ETIOLOGY/PATHOGENESIS

Idiopathic

- Although speculative, infectious etiology (e.g., bacterial) either as cause or as cofactor in disease suggested based on
 - Reported beneficial effects of trimethoprim-sulfamethoxazole therapy on initial course of disease
 - Histologic features of disease similar to that found in infectious diseases

CLINICAL ISSUES

Presentation

- May be systemic or localized
 - Extent of disease reflected in clinical manifestations such that limited or localized disease may be asymptomatic
 - Patients with systemic involvement always sick
- Disease may progress from localized to systemic involvement or may remain limited or even regress with treatment
- ELK classification of GPA includes: E = ear, nose, and throat involvement; L = lung involvement; K = kidney involvement
 - Patients with E or EL disease are considered to have limited form of GPA
 - Patients with ELK disease correspond to systemic GPA
 - Incidence of limited GPA varies from 29-58%
- Localized UADT GPA
 - Tends to affect men more than women
 - Exception in laryngeal WG seen predominantly in women
 - In UADT, most common site of occurrence is sinonasal region with nasal cavity > maxillary > ethmoid > frontal > sphenoid
 - Other sites of involvement include
 - Nasopharynx, larynx (subglottis), oral cavity, ear (external and middle ear, including mastoid), and salivary glands
 - Symptoms vary according to site of involvement, including

- Sinonasal tract: Sinusitis ± purulent rhinorrhea, obstruction, pain, epistaxis, anosmia, headaches
- Oral: Ulcerative lesion, gingivitis
- Ear: Hearing loss, pain
- Larynx: Dyspnea, hoarseness, voice changes
- Involvement of larynx most often subglottic region
 - 8-25% of patients with GPA will develop disease referable to larynx
 - Involvement of larynx seen more often in setting of preexisting disease elsewhere
 - Presentation with laryngeal GPA rare event

Laboratory Tests

- Important adjunct evaluation includes
 - Elevated antineutrophil cytoplasmic antibody (ANCA)
 - Elevated proteinase 3 (PR3)
- Elevated ANCA
 - Reported specificity for diagnosis of GPA from 85-98%
 - ANCA reactivity seen in form of cytoplasmic (c-ANCA) vs. perinuclear (p-ANCA) staining
 - GPA characteristically associated with c-ANCA and only infrequently with p-ANCA
 - c-ANCA of greater specificity than p-ANCA
 - Sensitivity of test varies with extent of disease
 - Patients with limited GPA have 50-67% c-ANCA positivity
 - Patients with systemic GPA have 60-100% positivity
 - Negative test does not rule out GPA
 - May be identified in other vasculitides
 - Inflammatory bowel disease and hepatobiliary diseases
 - ANCA titers not elevated in infections or in lymphomas
 - ANCA titers follow disease course
 - Titers revert to normal levels with remission and become elevated with recurrent or persistent disease
 - Decline in c-ANCA titer may lag behind clinical evidence of remission by up to 6-8 weeks
- PR3
 - PR3 is neutral serine proteinase present in azurophilic granules of human polymorphonuclear leukocytes and monocyte lysosomal granules
 - Serves as major target antigen of ANCA with cytoplasmic staining pattern (c-ANCA) in GPA
 - ANCA with specificity for PR3 characteristic for patients with GPA
 - Patients with GPA demonstrate significantly higher percentage of mPR3(+) neutrophils than healthy controls and patients with other inflammatory diseases
 - Detection of ANCA directed against PR3-ANCA is highly specific for GPA
 - ANCA positivity found only ~ 50% of patients with localized GPA, whereas PR3-ANCA positivity seen in 95% of patients with generalized GPA
 - Pathogenesis of vascular injury in GPA ascribed to ANCA directed mainly against PR3
 - Interaction of ANCA with neutrophilic ANCA antigens necessary for development of ANCA-associated diseases
 - ANCA bind to membrane-expressed PR3 and induce full-blown activation in primed neutrophils

Granulomatosis With Polyangiitis

- In patients with GPA, high expression of PR3 on surface of nonprimed neutrophils associated with increased incidence and rate of relapse
- ANCA-associated vasculitis (AAV) includes
 - GPA, microscopic polyangiitis (MPA), and allergic granulomatous angiitis (AGA)
 - Major target antigens of ANCA-associated vasculitis include PR3 and myeloperoxidase (MPO)
 - PR3-ANCA is marker for GPA; MPO-ANCA is related to MPA and AGA
 - ANCA appears to induce vasculitis by directly activating neutrophils
 - No immunoglobulins or complement components detected in vasculitis lesions
 - As such, AAV called pauci-immune vasculitis

Treatment

- Options, risks, complications
 - Once diagnosis and extent of disease is determined
 - Most patients receive combination of cyclophosphamide and prednisone for remission induction
 - Patients with limited disease treated with antibiotics (trimethoprim-sulfamethoxazole)
 - Rituximab therapy
 - Similar to daily cyclophosphamide treatment for induction of remission in severe ANCA-associated vasculitis
 - May be superior in relapsing disease
 - Patients with fulminating disease, especially with renal failure, treated with high doses of prednisone
 - Maintained until disease under control as evidenced by improved ESR, serum creatinine, or ANCA titer at time cyclophosphamide therapy begun
 - Prednisone continued until cyclophosphamide takes effect; occurs ~ 2-3 weeks or following initiation of therapy
 - Surgical intervention may be required in treating patients with progression of disease in UADT

Prognosis

- Treatment with cyclophosphamide and prednisone results in 75% complete remission rate
 - Achieved, although patients may experience 1 or more relapses from 3 months to 16 years after complete remission
 - Patients with GPA who experience remission are not necessarily cured of disease
 - Remain at risk for recurrences throughout their life
- Limited GPA responds well to cyclophosphamide &/or steroid therapy and has good prognosis
- Mortality rates of up to 28% have been reported
 - Major source of morbidity and mortality is renal or pulmonary insufficiency &/or complications of therapy (e.g., sepsis, drug-induced malignancies)
- Occasionally, spontaneous remissions may be seen with milder forms of disease when only 1, or a few organs, are involved (but not kidneys)

MACROSCOPIC

General Features

- Sinonasal area
 - Diffuse ulcerative and crusted lesions with tissue destruction
 - In advanced cases, septal perforation may be seen, resulting in saddle nose deformity
- Oral cavity
 - Ulcerative, destructive lesions often seen along palate and alveolar region
- Larynx
 - Subglottic stenosis with associated ulcerative lesions

MICROSCOPIC

Histologic Features

- Histologic features of GPA include classic triad of
 - Vasculitis, granulomatous inflammation, and tissue necrosis
 - In practice, finding classic histologic triad in single, or even series of biopsies, is very uncommon
 - Seen in only 16% of biopsies from patients with proven GPA
 - Requiring presence of all features in single biopsy in order to render diagnosis will result in nondiagnostic interpretation
 - Diagnosis can be suggested even when classic histologic changes not present in biopsy
 - Risk of underdiagnosing GPA when all classic histologic components are lacking
 - Risk of overdiagnosing GPA when excessive reliance placed on presence of minimal histologic changes
- **Vasculitis**
 - Involves small- to medium-sized arteries
 - Difficult to definitively identify histologically and often absent
 - Angiocentric (surrounding vessels) and angioinvasive (invading through vessel wall) potentially results in thrombosis of involved blood vessel
 - Vasculitis not limited to WG seen in infectious diseases (e.g., mucormycosis, aspergillosis)
- **Necrosis**
 - Ischemic- or geographic-type (multifocal necrobiosis) with basophilic smudgy appearance
 - Necrotic foci should be within stromal connective tissues and not along surface or edge of tissue specimen
 - Surface or superficial ulceration considered nonspecific ulceration, as seen in wide variety of lesions
- **Granulomatous inflammation**
 - Characterized by scattered or isolated multinucleated giant cells
 - Well-formed granulomas not typical feature of GPA
- **Inflammatory cell infiltrate**
 - Polymorphous inflammatory infiltrate composed of lymphocytes, histiocytes, and plasma cells
 - Less often comprised of eosinophils and polymorphonuclear leukocytes
 - Eosinophils may be numerous on occasion

- Microabscesses ± granuloma formation may be identified
- Bacterial superinfection of diseased mucosa, particularly *Staphylococcus aureus*, may complicate clinical picture

ANCILLARY TESTS

Histochemistry

- Elastic stains
 - May assist in identification of vasculitis
 - Disruption of elastic membranes
- Staining for microorganisms negative

Immunohistochemistry

- Immunoreactivity present for B-cell (CD20) and T-cell (CD3) markers
 - Indicative of benign (polyclonal) cellular population
- IgG4 immunostaining
 - Increased IgG4+ cells can be seen in sinonasal (or orbital/periorbital) biopsies of GPA
 - Biologic or clinical importance of increased IgG4+ cells in GPA involving head and neck region remains uncertain

DIFFERENTIAL DIAGNOSIS

Infectious Diseases

- Fungal, mycobacterial, parasitic are identified by light microscopy &/or special stains

Cocaine Abuse

- Characterized by foreign body giant cell reaction, including polarizable material

Churg-Strauss Disease

- Also referred to as allergic granulomatosis and vasculitis
- Characterized by asthma, systemic vasculitis, tissue and peripheral eosinophilia, nasal manifestations
 - These findings assist in differential diagnosis from GPA
 - Elevated ANCA levels reported in Churg-Strauss disease, so cannot be used to differentiate from GPA
 - Histology includes
 - Vasculitis of small- to medium-sized vessels with transmural inflammatory cell infiltrate (angioinvasion)
 - Inflammatory infiltrate predominantly includes eosinophils
 - Granulomatous vasculitis may be seen characterized by multinucleated giant cells within vessel wall (seen in ~ 38% of cases)
 - Eosinophilic microabscesses unrelated to blood vessels may be present

NK-/T-Cell Lymphoma, Nasal Type

- Cytologic characteristics of lymphoid infiltrate often permit distinction between GPA and NK-/T-cell lymphoma, nasal type
 - Cytologic atypia to outright malignant cells characteristic of NK-/T-cell lymphoma, nasal type
 - Lymphoid infiltrates in GPA lack appreciable degree of cytologic atypia
- Demonstration of monoclonality by immunohistochemistry or gene rearrangements by molecular analysis assists in recognition of lymphoma
- ANCA, PR3 negative

- Associated with Epstein-Barr virus [EBER(+)]

Diffuse Large B-Cell Lymphoma (DLBCL)

- Cytologic characteristics of lymphoid infiltrate often permit distinction between GPA and DLBCL
 - Presence of malignant cells
 - Lymphoid infiltrate in GPA lacks appreciable degree of cytologic atypia
- Demonstration of monoclonality by immunohistochemistry or gene rearrangements by molecular analysis assists in recognition of lymphoma
- ANCA, PR3 negative

Malignant Neoplasms

- Variety of nonhematolymphoid malignant neoplasms occur in sinonasal tract
 - Characterized by malignant neoplastic proliferation
 - GPA characterized by mixed inflammatory cell infiltrate, absence of malignant cells

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Elevated ANCA, PR3 important adjunct studies

Pathologic Interpretation Pearls

- Triad of vasculitis, granulomatous inflammation, and tissue necrosis seen in only 16% of proven GPA cases

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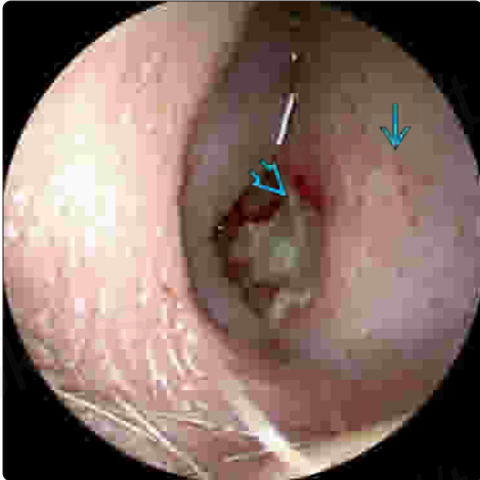
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Differential Diagnosis of Sinonasal Tract Wegener Granulomatosis

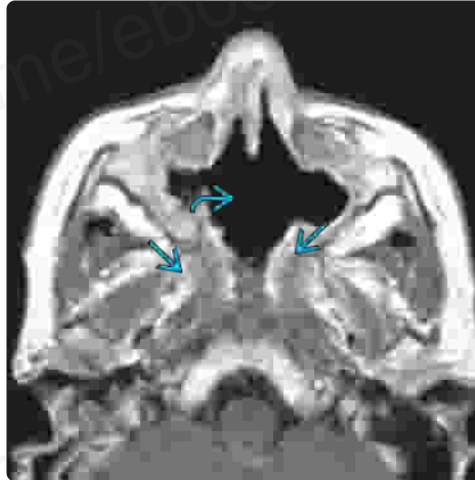
	GPA	NK-/T-Cell Lymphoma	DLBCL	Churg-Strauss
Gender/age	M > F; 4th-5th decades	M > F; 6th decade	M > F; 7th decade	M > F; wide age range (3rd-6th decades)
Location	Localized upper aerodigestive tract WG most common in nasal cavity > paranasal sinuses	Generally limited to SNT region; extra SNT represents higher stage tumor	Nasal cavity and 1 or more paranasal sinuses	Multisystem disease, including pulmonary, nasal, renal, skin, cardiac, and nervous system
Presentation	SNT: Sinusitis with or without purulent rhinorrhea, obstruction, pain, epistaxis, anosmia, headaches	Destructive process of midfacial region; may include septal perforation, palate destruction, orbital swelling	Nonhealing ulcer, epistaxis, facial swelling, pain, cranial nerve manifestations	Asthma, allergic rhinitis, evidence of eosinophilia, serum and tissue (e.g., eosinophilic pneumonia, eosinophilic gastroenteritis, other)
Serology	ANCA, PR3 positive	ANCA, PR3 negative; no specific serologic marker(s)	ANCA, PR3 negative; no specific serologic marker(s)	ANCA levels may or may not be present; PR3 negative
Histology	Polymorphous (benign) cellular infiltrate, vasculitis (angiocentric, angioinvasive), ischemic-type necrosis, isolated multinucleated giant cells (not well-formed granulomas)	In forme fruste, overtly malignant cellular infiltrate with angiocentricity and angioinvasion, ischemic-type necrosis; no giant cells or granulomas	Diffuse dyscohesive cellular proliferation of medium to large cells with large round to oval vesicular (noncleaved) nuclei, prominent nucleoli, increased mitotic activity, and necrosis	Polymorphous (benign) cellular infiltrate predominantly eosinophils; vasculitis, which may be granulomatous vasculitis (multinucleated giant cells in wall of involved blood vessels); eosinophilic microabscesses
Immunohistochemistry/molecular	Polymorphous and polyclonal; no gene rearrangement; EBER negative	CD56, CD2, cytoplasmic CD3e positive; T-cell markers (CD3) positive; EBER positive; gene rearrangements	Leucocyte common antigen and B-cell markers (CD20, CD79) positive; gene rearrangements	Polymorphous and polyclonal; no gene rearrangement
EBV	Negative	Strong association	Negative to weak association	Negative
Treatment	Cyclophosphamide and prednisone	Radiotherapy for localized disease; chemotherapy for disseminated disease	Radiotherapy &/or chemotherapy	Systemic corticosteroids
Prognosis	Limited disease associated with good to excellent prognosis and occasional spontaneous remissions; mortality related to complications of renal and pulmonary involvement	Overall survival 30-50%; local recurrence/relapse and systemic failure common	Dependent on stage; survival rates 35-60%	62% 5-year survival; increased morbidity and mortality due to cardiac involvement resulting in congestive heart failure or myocardial infarction

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Nasal Cavity Ulcerative Lesion

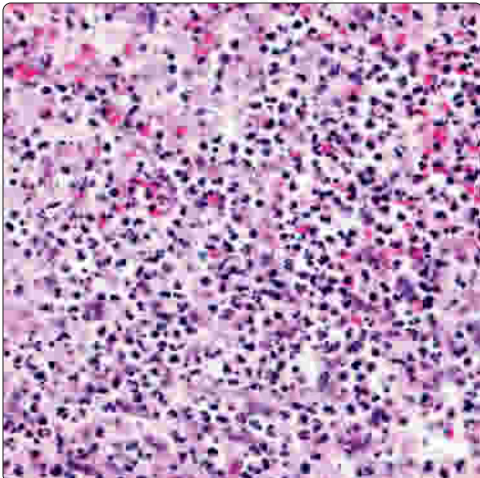


Extent of Disease and Septal Perforation



(Left) Clinical photograph of the anterior nasal cavity in a patient with granulomatosis with polyangiitis shows pale mucosa with a cobblestone appearance [1]; there is ulceration [2] posteriorly. (Right) Axial T1WI C+ MR reveals enhancement of the nodular peripheral soft tissue within the maxillary sinuses with involvement extending into the nasopharynx [3]. A large septal perforation [4] is present.

Neutrophilic Microabscess



Saddle Nose Deformity

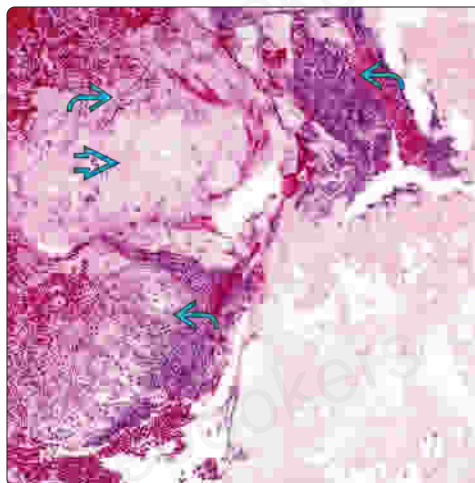


(Left) Neutrophilic microabscess formation (along with ischemic-type necrosis, vasculitis, and scattered giant cells) is another feature that can be seen in granulomatosis with polyangiitis. (Right) The clinical findings that can be seen in association with granulomatosis with polyangiitis include nasal septal destruction, as evidenced by the presence of saddle nose deformity. Other sinonasal tract symptoms may include sinusitis with or without purulent rhinorrhea, obstruction, pain, epistaxis, and anosmia.

Soft Tissue and Bone Destruction



Cartilage Involvement



(Left) Coronal bone CT shows extensive involvement of the sinonasal cavities by granulomatosis with polyangiitis. Extensive soft tissue with bone destruction and a septal perforation [1] is present. (Right) Histologically, septal destruction resulting in saddle nose deformity correlates to the presence of the inflammatory cell infiltrate [2] extending into septal elastic cartilage [3]. Similar histologic findings can be seen in relapsing polychondritis, which typically lacks ischemic necrosis, vasculitis, and giant cells.

Eosinophilic Angiocentric Fibrosis

KEY FACTS

TERMINOLOGY

- Rare, chronic, sclerosing, fibroinflammatory disorder of upper aerodigestive tract

ETIOLOGY/PATHOGENESIS

- Postulated to represent mucosal variant of granuloma faciale
- Recent evidence supports including eosinophilic angiocentric fibrosis (EAF) in spectrum of IgG4-related diseases

CLINICAL ISSUES

- Primarily involves nasal cavity
- Progressive airway (nasal) obstruction over several years
- Some patients have associated allergies, including allergic rhinitis, chronic urticaria, sensitivity to penicillin
- Surgery may be required in patients with airway obstruction
- Corticosteroids and antihistamines do not appear to be effective modes of treatment

- Disease progression stabilizes over time but typically not prior to development of airway obstruction

MICROSCOPIC

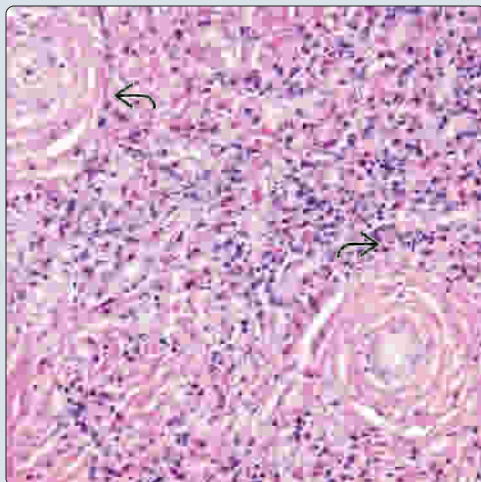
- Early phase
 - Eosinophilic perivascular infiltrate in lamina propria with eosinophilic angiitis
 - Eosinophils surround and extend into capillaries and venules (eosinophilic angiitis)
- Late phase
 - Dense fibrosis with layered onion skin-type perivascular fibrosis (angiocentric fibrosis)
 - Fibrosis is hypocellular, but areas of mixed inflammatory cells remain including eosinophils

TOP DIFFERENTIAL DIAGNOSES

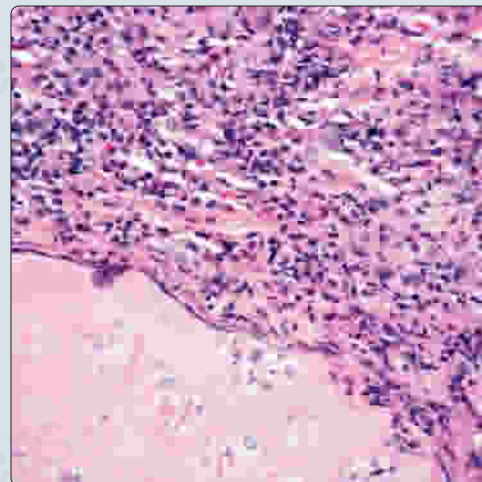
- Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis)
- Churg-Strauss disease
- Fibromatosis

Early Phase EAF

(Left) A mixed inflammatory cell infiltrate, including numerous eosinophils, is present and may be associated with small vessel walls [2], suggesting a small vessel angiitis. **(Right)** Mixed inflammation including eosinophils approximate but do not infiltrate nasal septal cartilage. Such features would contrast to findings that may be seen in relapsing polychondritis, which is characterized by infiltration of cartilage by an inflammatory cell infiltrate.

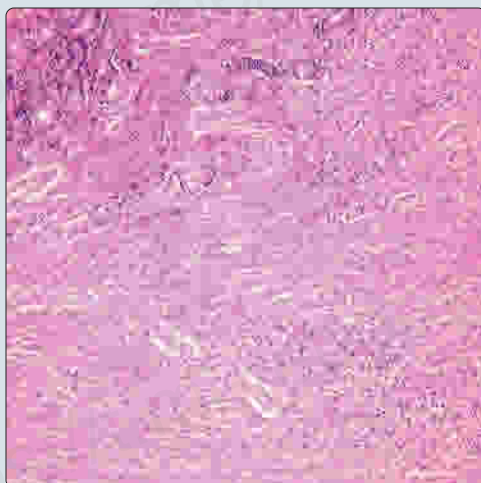


Early Phase EAF

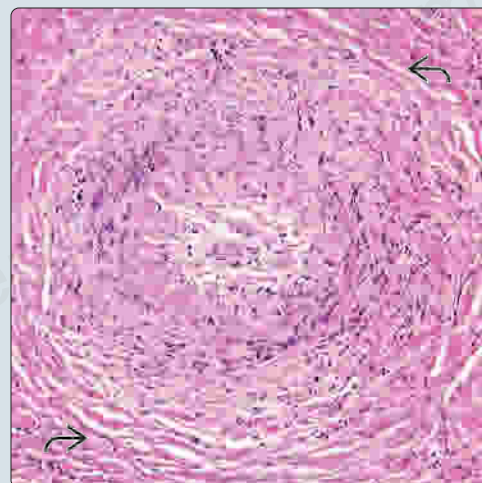


Late Phase EAF

(Left) Dense stromal fibrosis is a characteristic feature in the late phase of eosinophilic angiocentric fibrosis. The fibrosis is relatively hypocellular, but mixed inflammatory cells (including eosinophils) remain. **(Right)** Prominent stromal fibrosis with layered onion skin-type perivascular fibrosis [2] is a characteristic feature. Ischemic-type necrosis, granulomas, and multinucleated giant cells are absent.



Late Phase EAF



TERMINOLOGY

Abbreviations

- Eosinophilic angiocentric fibrosis (EAF)

Definitions

- Rare, chronic, sclerosing, fibroinflammatory disorder of upper aerodigestive tract

ETIOLOGY/PATHOGENESIS

Idiopathic

- No known etiology
- Postulated to represent mucosal variant of granuloma faciale
- Recent evidence supports including EAF in spectrum of IgG4-related diseases

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon
- Age
 - Adults
- Sex
 - Female > > male
 - All reported cases occurred in women

Site

- Primarily involves nasal cavity (unilateral or bilateral)
 - Septum > lateral wall
 - Rarely extends to paranasal sinuses (usually maxillary sinus) or orbit
- Rarely involves subglottic region

Presentation

- Progressive airway (nasal) obstruction over several years
 - Some patients have associated allergies, including allergic rhinitis, chronic urticaria, sensitivity to penicillin
- Pain, epistaxis uncommon

Laboratory Tests

- Nonspecific
 - PR3-ANCA levels not elevated
 - Erythrocyte sedimentation rate, urinalysis without abnormalities

Treatment

- Surgical approaches
 - Surgery may be required in patients with airway obstruction
- Drugs
 - Corticosteroids and antihistamines do not appear to be effective modes of treatment

Prognosis

- Disease progression stabilizes over time but typically not prior to development of airway obstruction

MICROSCOPIC

Histologic Features

- Early phase

- Eosinophilic perivascular infiltrate in lamina propria
 - Eosinophils surround and extend into capillaries and venules (eosinophilic angitis)
 - Plasma cells and mature lymphocytes may also be present
 - Thrombosis and ischemic-type necrosis are not identified
- Late phase
 - Characteristic feature is presence of dense fibrosis with layered onion skin-type perivascular fibrosis (angiocentric fibrosis)
 - Fibrosis is hypocellular, but areas of mixed inflammatory cells remain, including eosinophils
- In both phases, no evidence of ischemic-type necrosis, granulomatous inflammation, or multinucleated giant cells

ANCILLARY TESTS

Histochemistry

- Special stains for microorganisms are negative

DIFFERENTIAL DIAGNOSIS

Infectious Disease

- Microorganisms identified

Granulomatosis With Polyangiitis (Formerly Known as Wegener Granulomatosis)

- Presence of ischemic-type necrosis, vasculitis, &/or multinucleated giant cells
- Elevated serologic PR3-ANCA levels

Churg-Strauss Disease

- Characterized by asthma, systemic vasculitis, tissue and peripheral eosinophilia, nasal manifestations
- Vasculitis with transmural inflammation
 - Predominantly eosinophilic cell infiltrate
- Granulomatous vasculitis, including multinucleated giant cells found within vessel wall

Fibromatosis

- Dense fibrosis lacking features of EAF
- Beta-catenin (nuclear) reactivity; not found in EAF

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Sinonasal Inflammatory Polyp

KEY FACTS

TERMINOLOGY

- Nonneoplastic inflammatory swellings of sinonasal mucosa

ETIOLOGY/PATHOGENESIS

- Etiology linked to multiple factors, including but not limited to
 - Allergy (atopy)

CLINICAL ISSUES

- Most arise from lateral nasal wall or from ethmoid recess
- Nasal obstruction, rhinorrhea, and headaches
- Polypectomy
- ~ 50% of patients will have recurrence following surgery

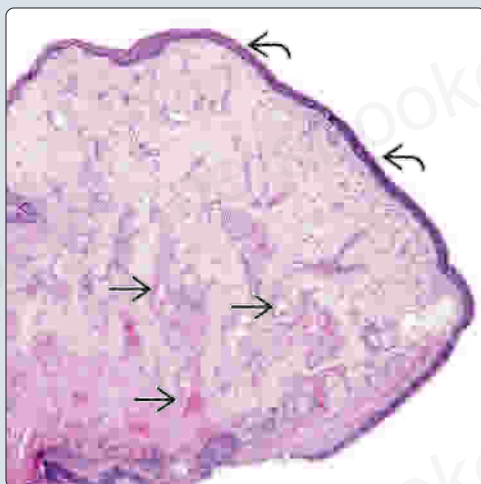
MICROSCOPIC

- Surface ciliated respiratory epithelium typically intact; may show squamous metaplasia
- Markedly edematous stroma noteworthy for absence of seromucous glands

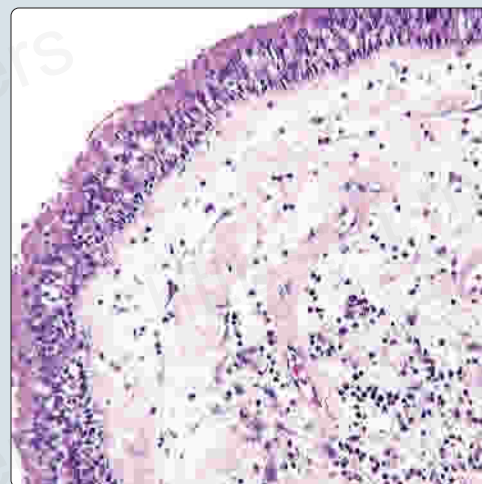
- Mixed chronic inflammatory cell infiltrate predominantly composed of eosinophils, plasma cells, and lymphocytes
- Secondary changes may include
 - Surface ulceration
 - Fibrosis
 - Infarction
 - Granulation tissue
 - Atypical stromal cells
 - Bizarre-appearing cells with enlarged, pleomorphic, and hyperchromatic nuclei, indistinct to prominent nucleoli, and eosinophilic to basophilic appearing cytoplasm
 - Typically, an ample amount of cytoplasm present such that there is low nuclear:cytoplasmic ratio, feature usually associated with benignancy.
 - Granuloma formation
 - Osseous &/or cartilaginous metaplasia

Sinonasal Inflammatory Polyp

(Left) Polypoid mass is seen with intact surface (respiratory) epithelium and underlying stroma characterized by edema, inflammatory infiltrate, increased vascularity, and absence of mucoserous glands. (Right) Higher magnification shows the intact ciliated respiratory epithelium and submucosal edematous stroma with mixed chronic inflammatory infiltrate, including mature lymphocytes, plasma cells, and eosinophils. These overall findings are characteristic and diagnostic.

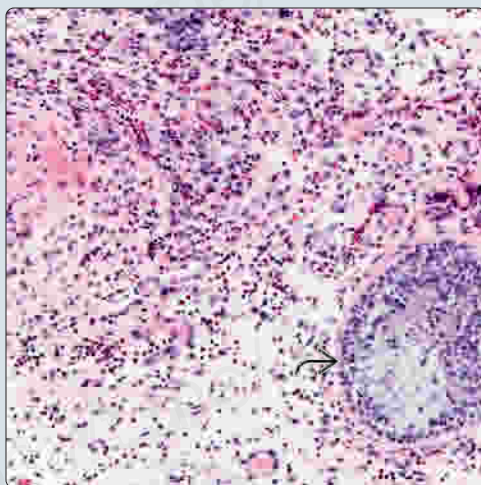


Higher Magnification



Prominent Eosinophilic Infiltrate

(Left) In this example, the submucosal inflammatory cell infiltrate is dominated by eosinophils, a finding that may correlate to a clinical history of asthma. Although generally devoid of seromucous glands, residual seromucous glands may be present. (Right) Mucous gland hyperplasia may potentially create diagnostic concern for a glandular neoplasm. The background alterations typically seen in inflammatory polyps and the absence of complex (back-to-back) growth seen in glandular neoplasms allow for differentiation.



Mucous Cell Hyperplasia



TERMINOLOGY

Definitions

- Nonneoplastic inflammatory swellings of sinonasal mucosa

ETIOLOGY/PATHOGENESIS

Multifactorial

- Etiology linked to multiple factors including
 - Allergy (atopy)
 - Infections
 - Cystic fibrosis
 - Diabetes mellitus
 - Aspirin intolerance
 - Familial

CLINICAL ISSUES

Epidemiology

- Age
 - Occurs in all ages but commonly seen in adults over 20 years old
 - Rarely seen in children less than 5 years old
 - Exception in patients with cystic fibrosis who develop nasal polyps in 1st and 2nd decades of life
- Sex
 - Equal gender distribution

Site

- Most arise from lateral nasal wall or ethmoid recess
 - May be unilateral or bilateral, single or multiple
- Not infrequently, involvement of both nasal cavity and paranasal sinuses

Presentation

- Nasal obstruction, rhinorrhea, and headaches
- Samter triad
 - Nasal polyps, asthma, and aspirin intolerance
- Rarely, may be associated with bone erosion, destruction, blindness

Endoscopic Findings

- Mulberry turbinate
 - Clinical term referring to swollen nasal turbinate tissue

Treatment

- Options, risks, complications
 - Identification and treatment of possible etiologic factor(s) is initial approach in treatment
- Surgical approaches
 - Polypectomy
 - Medial maxillectomy (Caldwell-Luc procedure) including removal of stalk for antrochoanal polyps
- Drugs
 - Patients with cystic fibrosis may respond to medical therapy, but surgical resection may be required

Prognosis

- ~ 50% of patients will have recurrence following surgery
 - Recurrence rates highest in patients with aspirin intolerance and asthma
- Development of functional endoscopic sinus surgery contributed to

- Decreasing morbidity of sinonasal surgery and recurrence of nasal polyposis in patients with cystic fibrosis
- Improving sinonasal-related symptomatology for asthmatic patients
- Systemic steroid treatment effective in decreasing polyp size and in controlling mucosal inflammation
 - Systemic steroid treatment may also contributed to prevention of recurrence

IMAGING

General Features

- Soft tissue densities, air-fluid levels, mucosal thickening, and opacification of paranasal sinuses
- When extensive, inflammatory polyps may expand and even destroy bone

MACROSCOPIC

General Features

- Polyps are soft, fleshy, polypoid lesions with myxoid or mucoid appearance

Size

- Vary in size, ranging up to several centimeters in diameter

MICROSCOPIC

Histologic Features

- Surface ciliated respiratory epithelium typically intact
 - May show squamous metaplasia
 - Basement membrane may be thickened and eosinophilic in appearance
- Stroma
 - Markedly edematous; noteworthy for absence of seromucous glands
 - Contains mixed chronic inflammatory cell infiltrate predominantly composed of eosinophils, plasma cells, and lymphocytes
 - Neutrophils may predominate in polyps of infectious origin
 - Bland-appearing fibroblasts and small to medium-sized blood vessels
 - Spaces containing watery-appearing fluid simulate appearance of lymphatic spaces, suggesting diagnosis of lymphangioma
 - Spaces lack endothelial cell lining
 - Prominent vascular component may be present
 - Variably termed angiomatous or angioectatic nasal polyps
 - May simulate appearance of neoplasm
- Secondary changes may include
 - Surface ulceration
 - Fibrosis
 - Infarction
 - Atypical stromal cells
 - Bizarre-appearing cells with enlarged, pleomorphic, and hyperchromatic nuclei, indistinct to prominent nucleoli, and eosinophilic to basophilic appearing cytoplasm

- Typically, ample amount of cytoplasm present such that there is low nuclear:cytoplasmic ratio, feature usually associated with benignancy
- Represent myofibroblasts
- Often localized to areas of injury, especially around thrombosed vessels
- Granulation tissue
- Osseous &/or cartilaginous metaplasia
- Glandular (mucous cell) hyperplasia
- Causes for granuloma formation include
 - Ruptured mucous cysts
 - Cholesterol granulomas
 - Reaction to intranasal injections (steroids) or inhalants
- Pseudogranulomas may be seen
 - Small patches of stromal nonedematous collagen with peripherally situated inflammatory cells

DIFFERENTIAL DIAGNOSIS

Infectious Diseases

- Absence of microorganisms in polyps

Schneiderian Papillomas

- Neoplastic epithelial proliferation characterized by
 - Markedly thickened epithelial proliferation comprised of
 - Squamous, transitional, &/or columnar cells with admixed mucocytes (goblet cells)
 - Intraepithelial mucous cysts
 - Endophytic (inverted) &/or exophytic growth

Respiratory Epithelial Adenomatoid Hamartoma

- Histopathologic changes dominated by presence of glandular proliferation composed of
 - Widely-spaced, small to medium-sized glands separated by stromal tissue

Nasopharyngeal Angiofibroma

- Neoplastic proliferation composed of variable admixture of
 - Slit-like vascular spaces lacking mural smooth muscle
 - Dense stromal fibrosis

Rhabdomyosarcoma

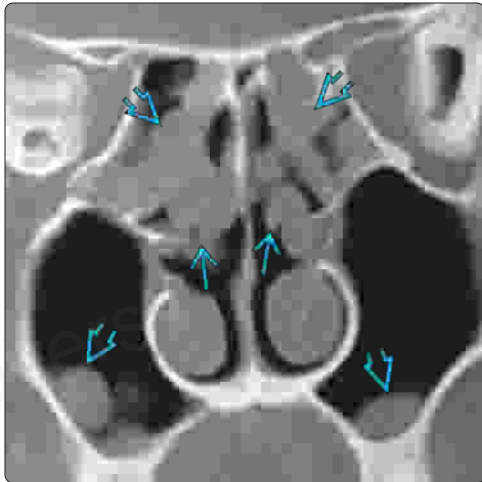
- Atypical stromal cells may be confused with malignant cells (rhabdomyoblasts)
- Cellular components consist of admixture of cell types including
 - Small undifferentiated (primitive-appearing) round or spindle-shaped cells with hyperchromatic nuclei and indistinct cytoplasm
 - Differentiated large round to oval cells with eosinophilic cytoplasm
 - Cross striations are rare in round cells but more apparent in spindle cell component
- Nuclear pleomorphism, increased mitotic activity, and necrosis are present
- Immunoreactivity for myogenic markers including
 - Desmin, myoglobin, myogenin

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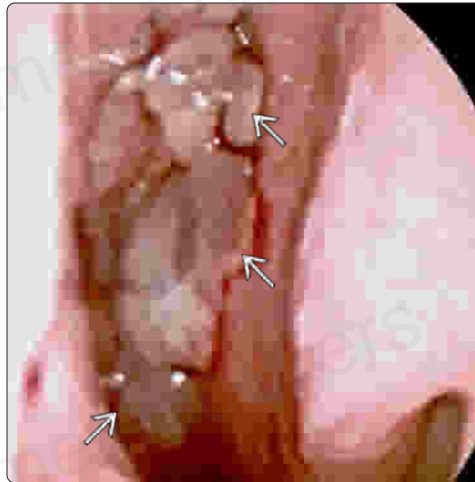
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CT Scan of Inflammatory Polyps

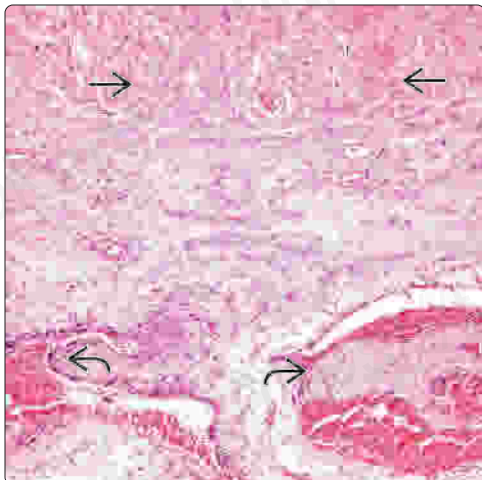


Endoscopic Appearance



(Left) Coronal bone CT shows typical appearance of sinonasal polyposis with multiple polypoid soft tissue masses within nasal cavity. (Right) Endoscopic photograph in a patient with sinonasal polyposis shows multiple grape-like, pale masses in the nasal cavity, characteristic of polyps.

Infarcted Inflammatory Polyp

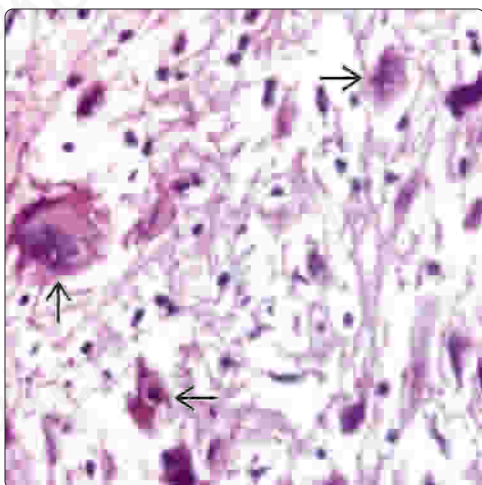


Cholesterol Granuloma Formation

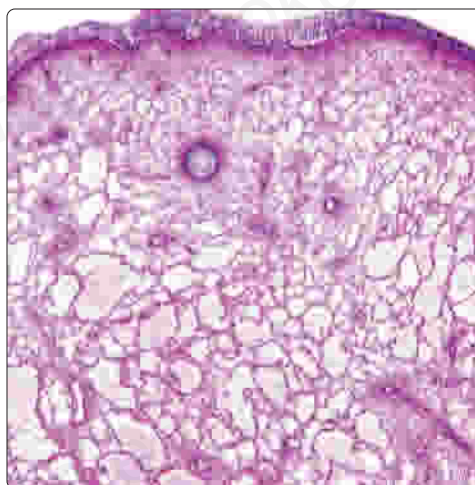


(Left) Thrombosed blood vessels with hemorrhage and infarction (not shown) can occur in traumatized sinonasal inflammatory polyps. (Right) Cholesterol granuloma formation in a polyp comprised of clear, needle-shaped spaces represent lipid from extravasated erythrocytes with associated multinucleated giant cells. Pigmented cells represent hemosiderin deposition, an indicator of past hemorrhage.

Atypical Stromal Cells



Lymphangiomatous Appearance



(Left) Atypical stromal cells represent myofibroblasts that may be mistaken for malignant cells potentially leading to a diagnosis of sarcoma. These cells tend to be localized in the polyp and occur in association with other reactive changes. (Right) Submucosal dilated spaces containing watery-appearing fluid simulate lymphatic spaces, suggesting a diagnosis of lymphangioma. In contrast to lymphangioma, the spaces lack an endothelial lining.

Antrochoanal Polyp

KEY FACTS

TERMINOLOGY

- Clinically distinctive sinonasal polyp originating from the medial maxillary sinus and extending via stalk through the maxillary ostium into nasal cavity

CLINICAL ISSUES

- Represents ~ 3-6% of all sinonasal polyps
- Primarily teenagers and young adults
- Generally presents as a single, unilateral polyp with nasal obstruction
- Complete surgical excision, including stalk, is treatment of choice
 - May recur if polyp, including stalk, is incompletely excised

MICROSCOPIC

- Similar to sinonasal polyps except for relative lack of mucous glands and eosinophilic inflammatory infiltrate
- Presence of atypical stromal cells

- Myofibroblastic origin and cellular component of wound healing
- Bizarre-appearing cells with enlarged pleomorphic and hyperchromatic nuclei, indistinct to prominent nucleoli, eosinophilic to basophilic cytoplasm
- Tend to cluster near areas of tissue injury (e.g., near thrombosed vascular spaces)
- Infarction, partial or complete, with variable hemorrhage


ANCILLARY TESTS

- **Positive:** Vimentin, actins (smooth muscle, muscle specific)
 - Pancytokeratin staining may be present
- **Negative:** Desmin, myoglobin, myogenin, MyoD1

TOP DIFFERENTIAL DIAGNOSES

- Nasopharyngeal angiofibroma
- Rhabdomyosarcoma

Multiple Nodular Polyp

(Left) Gross pathology photograph shows a resected antrochoanal polyp measuring ~ 6 cm in length. The polyp was extracted from a nasopharyngeal approach. Note the bulbous nasopharyngeal component that expands after leaving the maxillary antrum. (Right) This polyp shows an intact epithelium with a very fibrotic to edematous stroma. Note the complete lack of minor mucoserous glands. Many vessels are noted ; however, they do not arborize, nor do they show a spectrum of vessel types.

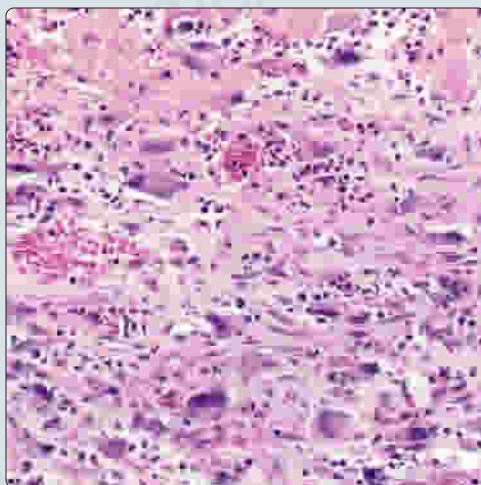


Large Polyp With Fibrosis and No Glands

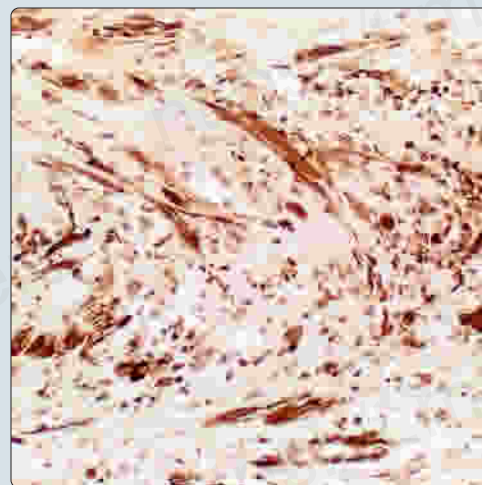


Stromal Atypia in Antrochoanal Polyp

(Left) This illustration on high power shows the reactive and atypical fibroblasts that are part of the stroma. There is associated hemorrhage and inflammation. These cells tend to aggregate around areas of injury. (Right) The myofibroblastic cells that comprise the atypical stromal cells are usually strongly and diffusely reactive with actins (smooth muscle actin shown), but are negative with desmin, myogenin, and MyoD1.



Myofibroblasts Stain Strongly With SMA



TERMINOLOGY

Abbreviations

- Antrochoanal polyp (ACP)

Definitions

- Clinically distinctive sinonasal polyp originating from the medial maxillary sinus and extending via stalk through the maxillary ostium into nasal cavity

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Despite correlation in up to 40% of cases with history of allergies, felt to be of inflammatory etiology

CLINICAL ISSUES

Epidemiology

- Incidence
 - Represents ~ 3-6% of all sinonasal polyps
- Age
 - Patients are younger than those with nasal polyps
 - Primarily teenagers and young adults
- Sex
 - Male > female

Site

- Medial wall of maxillary sinus and extending via stalk through ostium of maxillary sinus into nasal cavity
- Posterior extension to nasopharynx may result in obstruction and clinical suspicion of primary nasopharyngeal tumor
- May extend ("hang") into oropharynx and be identifiable through open mouth

Presentation

- Generally presents as a single, unilateral polyp with nasal obstruction
- May be associated with more typical sinonasal polyps
- Rarely may coexist with sphenchoanal polyp
 - Sphenchoanal polyps originate from sphenoid sinus, extending through sphenoid ostium into choana

Treatment

- Complete surgical excision to include stalk

Prognosis

- Cured following complete surgical excision
- May recur if polyp, including stalk, is incompletely excised
 - High recurrence rate in patients with allergies

MACROSCOPIC

Size

- Tend to be large; mean: 3-6 cm

MICROSCOPIC

Histologic Features

- Similar to sinonasal polyps except for relative lack of mucous glands and eosinophilic inflammatory infiltrate
- Subject to secondary changes resulting from chronic or subacute vascular compromise including

- Presence of atypical stromal cells
 - Myofibroblastic origin and cellular component of wound healing
 - Bizarre-appearing cells with enlarged pleomorphic and hyperchromatic nuclei, indistinct to prominent nucleoli, eosinophilic to basophilic cytoplasm
 - Tend to cluster near areas of tissue injury (e.g., near thrombosed vascular spaces)
 - May be confused with malignant cells (e.g., rhabdomyoblasts)
 - Localization to limited areas of lesion coupled with absence of increased nuclear to cytoplasmic ratio, increased mitoses, or cross striations preclude diagnosis of malignancy
- Infarction, partial or complete
 - Hemorrhage may be minimal or extensive
 - Associated reactive changes may include extensive neovascularization
 - Papillary endothelial hyperplasia may occur in conjunction with organizing thrombus
 - Presence of hemorrhage and reactive changes may result in bone erosion of lateral nasal cavity-medial maxillary sinus wall

ANCILLARY TESTS

Immunohistochemistry

- Atypical stromal cells
 - **Positive:** Vimentin, actins (smooth muscle, muscle specific)
 - Pancytokeratin staining may be present
 - **Negative:** Desmin, myoglobin, myogenin, MyoD1

DIFFERENTIAL DIAGNOSIS

Nasopharyngeal Angiofibroma

- Nasopharynx origin; spectrum of vessels, including smooth muscle walled and slit-like vascular spaces; stromal collagen

Rhabdomyosarcoma

- Sheet-like; cambium layer; atypical strap cells (rhabdomyoblasts); pleomorphism; mitoses; necrosis
- **Positive:** Desmin, myogenin, MyoD1, myoglobin

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KEY FACTS

TERMINOLOGY

- **REAH:** Benign acquired nonneoplastic overgrowth of indigenous glands of sinonasal tract and nasopharynx arising from surface epithelium
- **SH:** Benign acquired nonneoplastic overgrowth of indigenous glands of sinonasal tract and nasopharynx arising from submucosal seromucous gland
- **CORE hamartoma:** Related to REAH but has additional feature of chondroid tissue
- **NCH:** Composed of admixture of chondroid and stromal elements with cystic features analogous to chest wall hamartoma

CLINICAL ISSUES

- Majority occur in nasal cavity, especially posterior septum
- Involvement of other intranasal site; nasopharynx and paranasal sinuses occurs less often
- Conservative, but complete surgical excision is treatment of choice

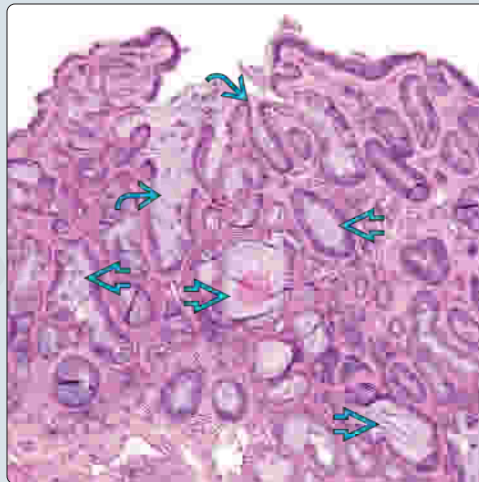
- Cured following surgical resection (endoscopic or open)

MICROSCOPIC

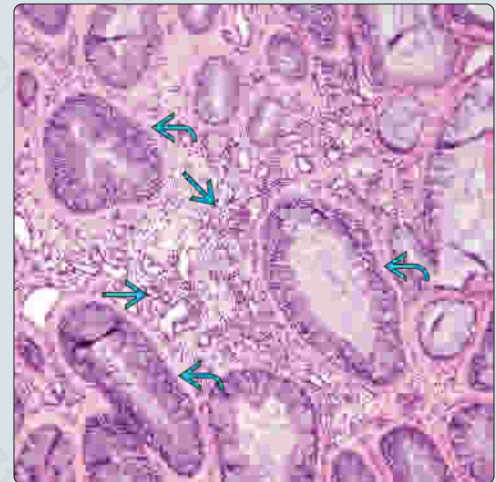
- **REAH:** Dominated by glandular proliferation arising in direct continuity with surface epithelium, which invaginates downward into submucosa often enveloped by eosinophilic basement membrane
- **SH:** Submucosal epithelial proliferation of small glands, serous acini, and tubules growing in clusters and lobules, although haphazard arrangement with larger glands and cysts may be seen
- **CORE hamartoma:** Similar features to REAH hamartomas but with intimate admixture of cartilaginous &/or osseous trabeculae
- **NCH:** Characterized by presence of nodules of cartilage varying in size, shape, and contour with varying differentiation
 - Loose spindle cell stroma or abrupt transition to hypocellular fibrous stroma are present at periphery of cartilaginous nodules

REAH, Surface Epithelial Invagination

(Left) Glandular proliferation made of widely spaced, small- to medium-sized glands separated by stromal tissue originating from surface epithelium & invaginating downward into the submucosa is shown. (Right) The glands here are round to oval, widely spaced, with a variable amount of intraluminal mucinous material & envelopment by a eosinophilic basement membrane, with fibrous to focally edematous stroma containing residual seromucinous glands and mixed chronic inflammatory cell infiltrate.

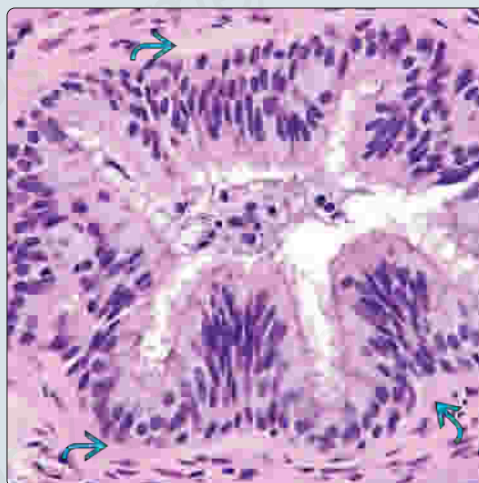


REAH, Glandular Proliferation

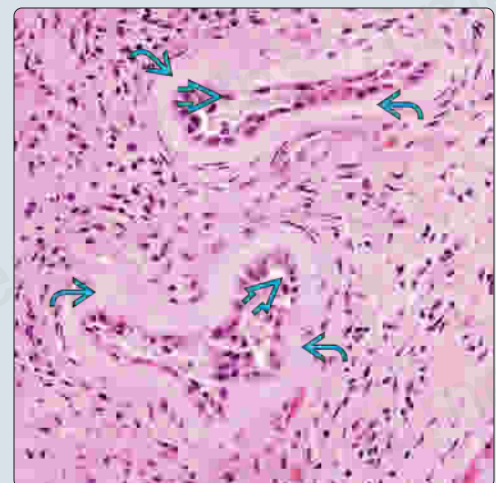


REAH, Periglandular Hyalinization

(Left) The glands seen here are round to oval, composed of multilayered ciliated respiratory epithelium with characteristic envelopment of the glands by a variably thickened, eosinophilic basement membrane. (Right) Atrophic glands include a single layer of flattened to cuboidal-appearing epithelium. The glands are enveloped by markedly thickened eosinophilic basement membranes.



REAH, Atrophic Changes



TERMINOLOGY

Abbreviations

- Respiratory epithelial adenomatoid hamartoma (REAH)
- Seromucinous hamartoma (SH)
- Chondroosseous and respiratory epithelial (CORE) hamartoma
- Nasal chondromesenchymal hamartoma (NCH)

Synonyms

- Glandular hamartoma
- Nasal hamartoma

Definitions

- **REAH:** Benign acquired nonneoplastic overgrowth of indigenous glands of sinonasal tract and nasopharynx
 - Arising from surface epithelium
 - Devoid of ectodermal, neuroectodermal, &/or mesodermal elements
- **SH:** Benign acquired nonneoplastic overgrowth of indigenous glands of sinonasal tract and nasopharynx
 - Arising from submucosal seromucous gland
 - Devoid of ectodermal, neuroectodermal, &/or mesodermal elements
- **CORE hamartoma**
 - Related to REAH but has additional feature of chondroid tissue
- **NCH:** Tumefactive process of sinonasal tract
 - Composed of admixture of chondroid and stromal elements with cystic features analogous to chest wall hamartoma
 - Histologic similarities to REAH and CORE hamartomas; may be within spectrum of same lesion type

ETIOLOGY/PATHOGENESIS

Idiopathic

- No association with any specific etiologic agent

Developmental

- REAH may arise in background of inflammatory polyps
 - Raises possible developmental induction secondary to inflammatory process
- SH reported in some patients to be associated with chronic sinusitis, inflammatory polyps, rheumatoid arthritis, and Parkinson disease
- NCH reported association with pleuropulmonary blastoma reported in small subset of patients

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare lesions
- Age
 - **REAH**
 - Occurs in adult patients
 - Range: 3rd-9th decades; median in 6th decade
 - **SH**
 - Range: 2nd-9th decades
 - **CORE hamartoma**
 - Range: 2nd-8th decades

NCH

- Most lesions occur in newborns within first 3 months of life but may occur in 2nd decade of life
 - ◻ Occasionally in adults

Sex

- **REAH and CORE hamartoma**
 - Equal gender distribution
- **SH and NCH**
 - Male > female

Site

- Majority occur in nasal cavity, particularly posterior nasal septum
 - Involvement of other intranasal sites occurs less often and may be identified
 - Along lateral nasal wall, middle meatus, and inferior turbinate
- Other sites of involvement include nasopharynx, ethmoid sinus, and frontal sinus
- Majority of lesions are unilateral, but bilateral lesions seen in ~ 25%

Presentation

- **REAH and SH**
 - Clinical presentation may include 1 or more of the following symptoms
 - Nasal obstruction, nasal stuffiness, epistaxis, and chronic (recurrent) rhinosinusitis; associated complaints include allergies
 - Symptoms may occur over months to years
 - Nondestructive lesion
- **CORE hamartoma**
 - Polypoid mass lesion
- **NCH**
 - Respiratory difficulty and intranasal mass or facial swelling may be present
 - May erode into cranial cavity (through cribriform plate area), clinically simulating appearance of meningoencephalocele

Treatment

- Surgical approaches
 - Conservative, but complete surgical excision treatment of choice

Prognosis

- Cured following surgical resection (endoscopic or open)
- Report of malignant transformation in adult with NCH

MACROSCOPIC

General Features

- Typically polypoid or exophytic with rubbery consistency, tan-white to red-brown appearance

Size

- May measure up to 6 cm in greatest dimension

MICROSCOPIC

Respiratory Epithelial Adenomatoid Hamartoma

- Changes dominated by presence of glandular proliferation composed of widely spaced, small- to medium-sized glands separated by stromal tissue
 - In areas, glands are seen arising in direct continuity with surface epithelium, which invaginate downward into submucosa
 - Glands are round to oval, composed of multilayered ciliated respiratory epithelium often with admixed mucin-secreting (goblet) cells
 - Glandular dilatation distended with mucus can be seen
- Characteristic finding includes presence of stromal hyalinization with envelopment of glands by thick, eosinophilic basement membrane
- Atrophic glandular alterations may be present in which glands are lined by single layer of flattened to cuboidal-appearing epithelium
- Edematous or fibrous stroma containing mixed chronic inflammatory cell infiltrate
- Additional findings may include
 - Alterations of inflammatory sinonasal polyp(s)
 - Hyperplasia &/or squamous metaplasia of surface epithelium unrelated to adenomatoid proliferation
 - Osseous metaplasia
 - Rare association with
 - Schneiderian papilloma, inverted type
 - Solitary fibrous tumor

Seromucinous Hamartoma

- Submucosal epithelial proliferation of small glands, serous acini, and tubules growing in clusters and lobules, although haphazard arrangement with larger glands and cysts are seen
 - Serous glands may be densely packed with back-to-back appearance that may resemble cribriform pattern of growth
 - Glands lined by low cuboidal to flat epithelium cells, with round to oval nuclei and variable amount of basophilic to eosinophilic to clear-appearing cytoplasm
 - Absence of significant nuclear pleomorphism, increased mitotic activity, and necrosis
 - Lack significant mucinous cell component, although focal mucinous change may be found
- Changes similar to those of REAH may be present, including
 - Invagination of surface respiratory epithelium with focal merging with glandular proliferation
 - Periglandular hyalinization

Chondroosseous and Respiratory Epithelial Hamartoma

- Similar features to REAH hamartomas but in addition
 - Intimately associated admixture of cartilaginous &/or osseous trabeculae
 - Spectrum of chondroosseous differentiation can be found, including immature-appearing mesenchyme to well-developed bony trabeculae in myxoid to fibrous stroma
 - REAH components present but less prominent

Nasal Chondromesenchymal Hamartoma

- Characterized by presence of nodules of cartilage varying in size, shape, and contour
 - Degree of differentiation varies with some nodules appearing similar to chondromyxomatous nodules of chondromyxoid fibroma to nodules of well-differentiated cartilage
- Loose spindle cell stroma or abrupt transition to hypocellular fibrous stroma are present at periphery of cartilaginous nodules
- Chondromesenchymal elements are relatively cellular and immature
- Other findings include
 - Myxoid to spindle cell stroma
 - Fibroosseous proliferation with cellular stromal component
 - Ossicles or trabeculae of immature (woven) bone
 - Focal, osteoclast-like giant cells in stroma
 - Erythrocyte-filled spaces resembling those of aneurysmal bone cyst
 - Mature adipose tissue can be present
 - Proliferating epithelial elements are not prominent feature

ANCILLARY TESTS

Immunohistochemistry

- REAH
 - Glandular proliferation (surface &/or submucosal)
 - Reactive for cytokeratins, including AE1/AE3, CAM5.2, CK7; **negative**: CK20 and CDX-2
 - p63 of basal (myoepithelial) cells present but may be absent
 - Absence of p63 positive does not confer diagnosis of adenocarcinoma
 - S100 protein may or may not be reactive
 - Ki-67 (MIB1) staining is either absent or shows very low proliferation rate (1-2%)
- SH
 - Seromucinous glands
 - Reactive for cytokeratins, including CK7, CK17, CK19, and high-molecular weight cytokeratin (HMWK) but **negative**: CK14 and CK20
 - p63 negative but in any given case may be positive
 - Limited S100 protein staining
 - Collagen type IV and laminin staining present around glandular proliferation
 - Ki-67 (MIB1) staining is either absent or shows very low proliferation rate (1-2%)
- NCH
 - Cartilaginous nodules and mesenchymal stromal component S100 protein staining
 - Spindle cell stroma vimentin and smooth muscle actin reactivity; muscle specific actin (HHF-35) may be present
 - Presence of actin reactivity supports myofibroblastic differentiation

Genetic Testing

- REAH
 - Reported mean fractional allelic loss (FAL) of 31%

- Higher than chronic sinusitis but not as high as sinonasal adenocarcinoma
- Suggests REAH may be benign neoplasm rather than hamartoma
- SH
 - DNA mutation analysis show higher mutation rate in comparison to normal seromucinous glands
 - Supportive of benign process, although no indications whether supportive of nonneoplastic or neoplastic lesion
 - Suggested similarities between SH and microglandular adenosis of breast
- NCH
 - Novel 12;17 translocation, t(12;17)(q24.1;q21) identified as sole reported anomaly
 - Occurred in single 11-year-old boy with past medical history of pleuropulmonary blastoma

DIFFERENTIAL DIAGNOSIS

Sinonasal Inflammatory Polyp

- Polypoid lesion characterized by stromal changes, including edema and mixed inflammatory cell infiltrate
- Typically lacks glandular proliferation as seen in REAH hamartoma
 - Rarely may include seromucous gland hyperplasia
- Surface epithelial alterations may include squamous metaplasia

Schneiderian Papillomas

- Surface epithelial proliferation with endophytic (inverted) or exophytic growth
- Lacks glandular proliferation as seen in REAH hamartoma

Nasopharyngeal Angiofibroma

- Neoplasm comprised of admixture of fibrous stromal component and benign endothelial-lined vascular component

Sinonasal Adenocarcinoma, Nonintestinal Nonsalivary Type(s)

- Glandular neoplasm characterized by
 - Complex growth (back-to-back glands) lacking lobular architecture
 - Glands lined by single cell type
 - Usually well-differentiated neoplasm lacking significant nuclear pleomorphism, increased mitoses, necrosis
 - Typically submucosal glandular proliferation lacking continuity to surface epithelium
 - Immunohistochemical staining of no diagnostic utility in differentiating adenocarcinoma from REAH or SH
 - p63 and other myoepithelial markers may be present or absent in hamartomas as well as in adenocarcinomas
 - Cannot be used to discriminate between hamartomas and adenocarcinoma

Biphenotypic Sinonasal Sarcoma

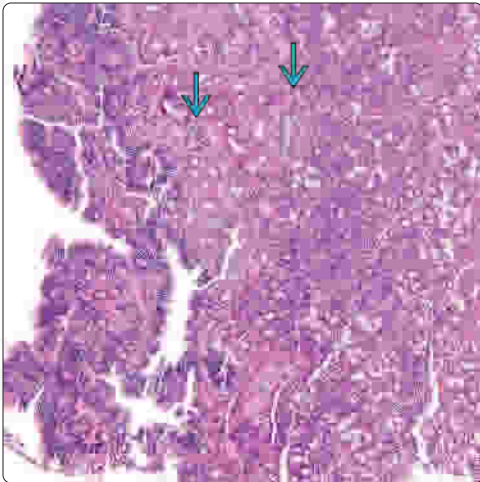
- Often includes benign epithelial (glandular) component that may suggest REAH
- Presence of spindle cell component with concomitant neural and myogenic differentiation contrasts with REAH

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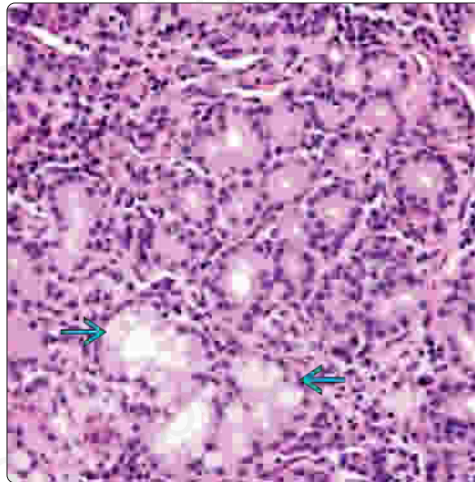
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Sinonasal Hamartomas				
	REAH	SH	CORE Hamartoma	NCH
Age/gender	M > F; 3rd-9th decades; median: 6th decade	M > F; 2nd-9th decade M = F	M = F; 2nd-8th decades	M > F; most occur in newborns within first 3 months of life, but may occur in 2nd decade and occasionally in adults
Site(s) of occurrence	Posterior nasal septum; involvement of other intranasal sites occurs less often; other sites may include nasopharynx, ethmoid sinus, frontal sinus	Posterior nasal septum; may occur in lateral nasal wall, paranasal sinuses, nasopharynx	Nasal cavity most common; other sites include nasopharynx, ethmoid sinus, sphenoid sinus	Intranasal mass or facial swelling; may erode into cranial cavity (through cribriform plate area)
Histology	Glandular proliferation arise in direct continuity with surface epithelium, which invaginate downward into submucosa; glands are round to oval composed of multilayered ciliated respiratory epithelium often with admixed mucin-secreting (goblet) cells; characteristic finding is presence of stromal hyalinization with envelopment of glands by thick, eosinophilic basement membrane	Serous gland proliferation with retention of lobular architecture; glands lined by low cuboidal to flat epithelium cells; invagination of surface respiratory epithelium may be seen with at least focal merging with glandular proliferation; periglandular hyalinization may also be present; lack significant mucinous cell component, although focal mucinous change may be found	Histologic features of REAH (although adenomatoid components tend to be of less prominent) and intimate association with cartilaginous &/or osseous	Nodules of cartilage and loose spindle cell stroma or abrupt transition to hypocellular fibrous stroma present at periphery of cartilaginous nodules
IHC	Cytokeratin (+) (AE1/AE3, CAM5.2, CK7); negative for CK20 and CDX-2; basal (myoepithelial) cells p63(+) but may be absent; S100 may or may not be positive; low- proliferation rate	Seromucinous glands reactive for cytokeratins (CK7, CK17, CK19), HMWK; negative for CK14, CK20; p63, calponin, MSA typically negative but in any given case may be positive; S100 protein staining is limited to seromucinous glands; low-proliferation rate	None reported	Cartilaginous nodules and mesenchymal stromal component S100 protein staining; spindle cell stroma vimentin and smooth muscle actin reactivity; muscle specific actin (HHF-35) may be present
Molecular findings	Increased fractional allelic loss	Higher mutation rate in comparison to normal seromucinous glands	None reported	None reported

SH, Seromucinous Gland Proliferation With Foci of REAH

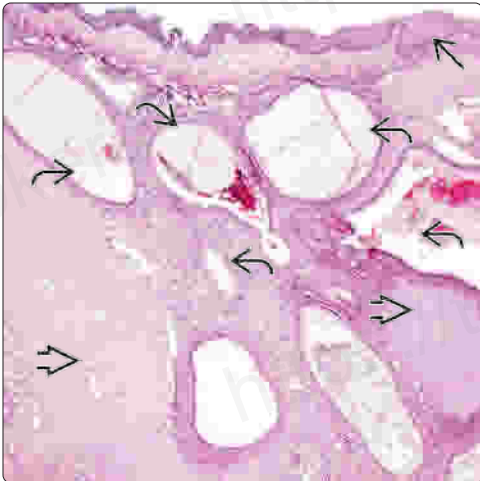


SH, Focal Mucinous Cells



(Left) Exophytic lesion, with submucosal glandular proliferation composed of serous and mucous acini with diffuse growth, is shown. Areas similar to those of REAH, including invagination of the surface respiratory epithelium merging with the glandular proliferation and periglandular hyalinization [1], may be seen. (Right) Predominant serous acinar proliferation with focal mucous cells [2] is seen. Serous glands may be densely packed with back-to-back appearance that may suggest a cribriform pattern of growth.

CORE Hamartoma, Glands and Cartilage



CORE Hamartoma, Glands and Cartilage

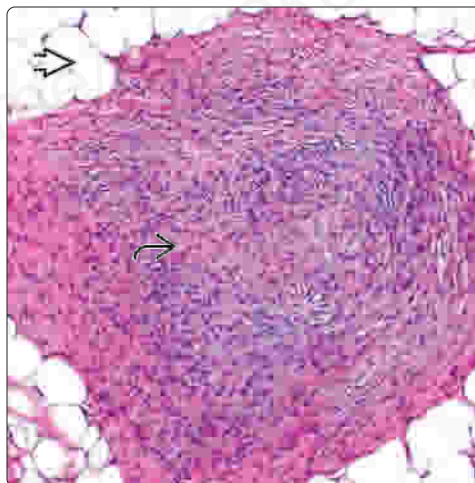


(Left) Chondroosseous and respiratory epithelial (CORE) hamartoma includes a submucosal proliferation of glands [1] that are less prominent compared to REAH, as well as lightly eosinophilic-appearing cartilage [2]. Note the surface epithelial squamous metaplasia [3]. (Right) At higher magnification, CORE hamartomas show an admixture of glands [1] and cartilaginous nodules [2]. A zonal-type phenomenon of the cartilage resembling endochondral ossification (not shown) may be present.

NCH, Bone and Adipose Tissue



NCH, Cellular Nodule



(Left) A nasal chondromesenchymal hamartoma (NCH) composed of a submucosal proliferation of adipose tissue [1], bony trabeculae [2], and cellular nodules [3] is shown. Residual seromucous glands are present [4]. (Right) A rounded myxochondroid-appearing cellular nodule composed of bland, spindle-shaped cells [1] is shown. It is surrounded by adipose tissue [2]. Additional findings (not shown) included cartilaginous nodules, bony trabeculae, and seromucous glands.

KEY FACTS

TERMINOLOGY

- Distinct clinicopathologic entity characterized by
 - Expansion of sinus cavity due to obstruction of outflow tract (ostium or duct) resulting in cystic lesion of paranasal sinus
 - Diagnosis requires correlation between clinical, radiographic, and pathologic findings, as histopathologic findings alone are nonspecific
 - Expansion of bony walls of sinus is sine qua non for paranasal sinus mucocele

ETIOLOGY/PATHOGENESIS

- Thought to occur as result of increase in pressure within a given sinus secondary to blockage of sinus outlet (ostium)
 - Most often result of inflammatory or allergic process

CLINICAL ISSUES

- > 90% occur in frontal and ethmoid sinuses

- Symptoms depend on site of involvement as well as direction, extent of expansion
 - Pain, facial swelling or deformity, visual disturbances
- Complete surgical excision is treatment of choice
- Excellent with long-term control

IMAGING

- Opacification of involved sinus
- Erosion &/or destruction of sinus walls with loss of typical scalloped outline along mucoperiosteum

MACROSCOPIC

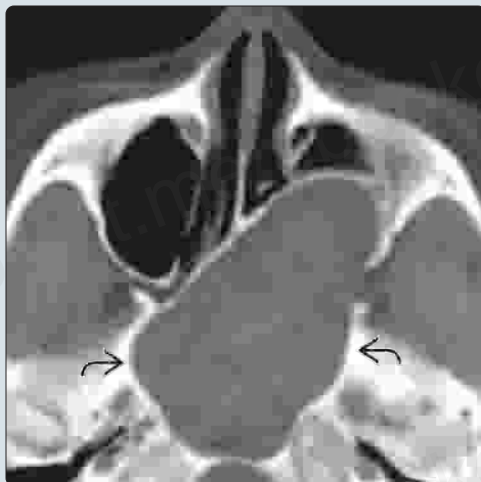
- **Internal:** Herniation of cyst into submucosal tissue adjacent to bony wall of sinus
- **External:** Herniation of cyst through bony wall of sinus with extension into subcutaneous tissue or into cranial cavity

MICROSCOPIC

- Cysts lined by flattened, pseudostratified, ciliated, columnar epithelium

Sinonasal Mucocele, Imaging Findings

(Left) Axial CT demonstrates an airless and grossly expanded sphenoid sinus with smooth expansion of the bony walls [A] and areas of bone erosion with extension into the medial and posterior orbit. (Right) Axial NECT reveals a low-density, expansile, left ethmoid mucocele. The lamina papyracea is remodeled, and there is mass effect on the medial rectus muscle [B].

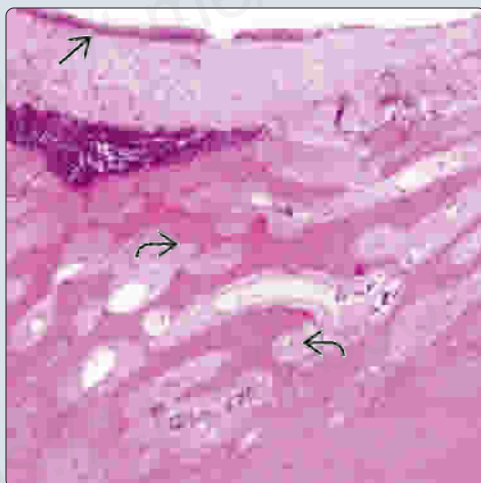


Sinonasal Mucocele, Imaging Findings

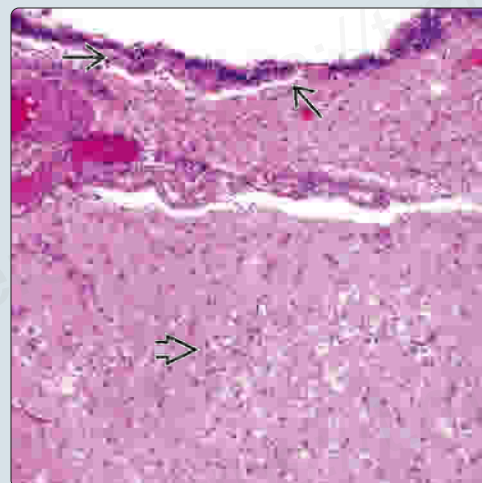


Sinonasal Mucocele, Histologic Features

(Left) Histologic features associated with an internal mucocele include a respiratory epithelial-lined cyst [A] lying near the bony wall of the sinus [B], as shown. The bone shows reactive changes. Clinical and radiologic correlation is required to confirm the diagnosis. (Right) External mucocele with herniation into the cranial cavity shows the respiratory epithelial-lined cyst [C] overlying central nervous system tissue [D].



Sinonasal Mucocele, Histologic Features



TERMINOLOGY

Definitions

- Distinct clinicopathologic entity characterized by
 - Expansion of sinus cavity due to obstruction of outflow tract (ostium or duct) resulting in cystic lesion of paranasal sinus
 - Diagnosis requires correlation between clinical, radiographic, and pathologic findings, as histopathologic findings alone are nonspecific
 - Expansion of bony walls of sinus is sine qua non for paranasal sinus mucocele

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Thought to occur as result of increase in pressure within a given sinus secondary to blockage of sinus outlet (ostium)
 - Most often result of inflammatory or allergic process
- Additional factors implicated include trauma, prior surgery, or neoplasm

CLINICAL ISSUES

Epidemiology

- Age
 - Occurs in all age groups
- Sex
 - Equal gender distribution

Site

- > 90% occur in frontal and ethmoid sinuses
 - Frontonasal duct is relatively long and narrow
 - Easily obstructed, especially following surgery to this region
- Maxillary sinus uncommonly involved (5-10%)
- Sphenoid sinus involvement considered rare

Presentation

- Chronic process with signs and symptoms occurring over time rather than acutely
- Symptoms depend on site of involvement as well as direction, extent of expansion
 - Pain
 - Facial swelling or deformity
 - Proptosis, exophthalmos, visual disturbances (e.g., diplopia, loss of vision, sudden blindness), optic neuropathy
 - Rhinorrhea, nasal obstruction

Treatment

- Surgical approaches
 - Complete surgical excision is treatment of choice
 - Trend toward transnasal endoscopic management

Prognosis

- Excellent with long-term control
 - Near zero recurrence rates
- Complications may include superimposed infection (pyocele), meningitis, brain abscess

IMAGING

Radiographic Findings

- Opacification of involved sinus
- Erosion &/or destruction of sinus walls with loss of typical scalloped outline along mucoperiosteum
- Abnormal radiolucency due to loss of bone
- Sclerosis of adjacent bone
- Cavity manifests smoothly contoured, expanded wall with reactive bony thickening
- Radiographic picture can be highly characteristic based on
 - Strikingly rounded appearance, presence of homogeneous mucoid contents

MACROSCOPIC

General Features

- 2 types of mucoceles are identified
 - **Internal**
 - Herniation of cyst into submucosal tissue adjacent to bony wall of sinus
 - **External**
 - Herniation of cyst through bony wall of sinus with extension into subcutaneous tissue or into cranial cavity

MICROSCOPIC

Histologic Features

- Cysts lined by flattened, pseudostratified, ciliated, columnar epithelium
- In longstanding cases, squamous metaplasia may be present
 - Metaplastic changes uncommon
- Reactive bone formation lying in proximity to cyst epithelium
- Variable chronic inflammatory cell infiltrate may be present
- Additional changes may include
 - Fibrosis, granulation tissue, hemorrhage, cholesterol granuloma
 - Central nervous tissue can be seen if herniation into cranial cavity

DIFFERENTIAL DIAGNOSIS

Mucus Retention Cyst (a.k.a. Salivary Mucocele)

- Cystic lesion of minor salivary glands characterized by well-circumscribed, submucosal mucus-filled, epithelial-lined cyst

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Extranodal Sinus Histiocytosis With Massive Lymphadenopathy

KEY FACTS

TERMINOLOGY

- Idiopathic histiocytic proliferative disorder characterized by lymph node-based disease
 - Extranodal manifestations occur with upper respiratory tract among more common sites of involvement

ETIOLOGY/PATHOGENESIS

- Etiology remains obscure
 - Infectious etiology has been suggested as cause, but infectious agent has never been isolated
- Although some studies implicated SHML as being IgG4-related disease, it is not believed to belong within spectrum of IgG4-related diseases

CLINICAL ISSUES

- Head and neck region represents one of more common extranodal areas involved
 - Predilection for sinonasal tract
- Sinonasal symptoms relate to nasal obstruction

- No ideal treatment
 - For airway compromise, treatment directed at alleviating obstruction, requiring surgical intervention
- Considered indolent, self-limiting disease

MICROSCOPIC

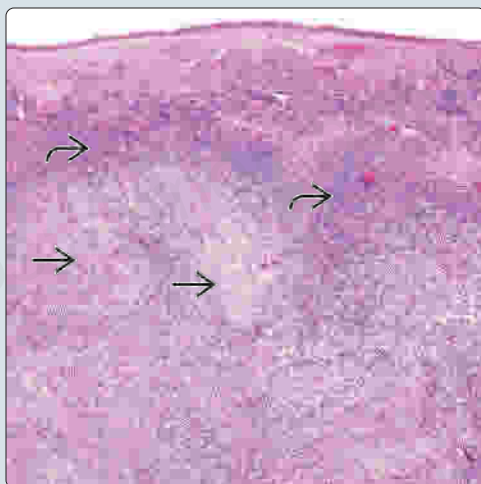
- Submucosal lymphoid aggregates associated with pale-appearing areas composed of histiocytes and plasma cells
- Lymphoid aggregates composed of mature lymphocytes and histiocytic cells impart mottled appearance
- Histiocytes appear in clusters or nests
 - Lack atypical features
 - Characteristically demonstrate emperipolesis
 - Nuclei lack nuclear lobation, indentation, or longitudinal grooving

ANCILLARY TESTS

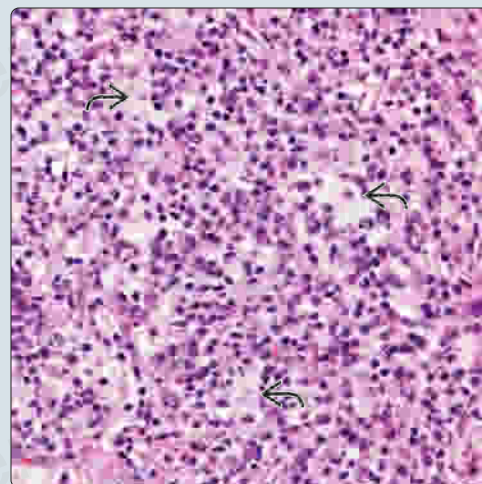
- SHML cells diffusely S100 protein positive but CD1a and Langerin negative

ESHML of Sinonasal Tract

(Left) Sinonasal tract ESHML shows the presence of a submucosal inflammatory cell infiltrate that includes lymphoid aggregates alternating with pale-appearing areas, creating a mottled appearance. (Right) The presence of a densely cellular mixed inflammatory cell infiltrate, including plasma cells and mature lymphocytes, may overrun and obscure the histiocytic cells, potentially creating difficulties in recognizing them and in the diagnosis of (extranodal) sinus histiocytosis with massive lymphadenopathy.

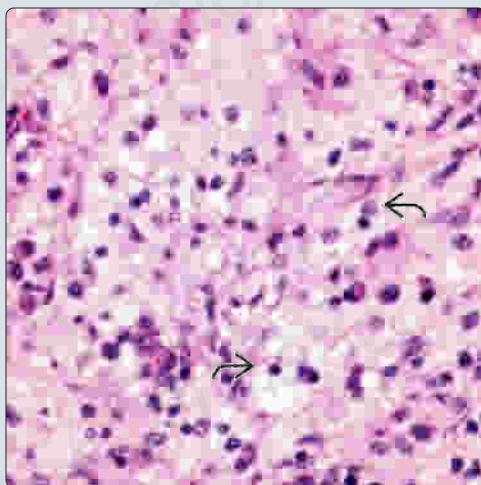


Histiocytic Cells in ESHML

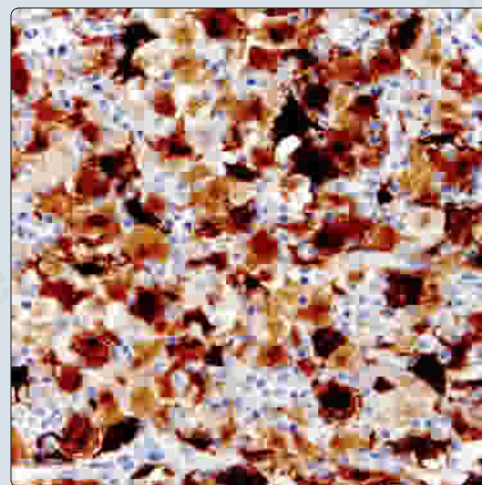


Histiocytic Cells With Emperipolesis

(Left) The histiocytic cells of SHML are composed of round nuclei with abundant clear to lightly eosinophilic cytoplasm that may engulf mononuclear cells. Such findings, referred to as emperipolesis, are less commonly seen in extranodal as compared to nodal-based disease. (Right) The histiocytes in SHML are diffusely immunoreactive for S100 protein but are CD1a and Langerin negative (not shown). The absence of CD1a and Langerin reactivity excludes a diagnosis of Langerhans cell histiocytosis.



S100 Protein Immunoreactivity



TERMINOLOGY

Abbreviations

- Extranodal sinus histiocytosis with massive lymphadenopathy (ESHML)
- Sinus histiocytosis with massive lymphadenopathy (SHML)

Synonyms

- Rosai-Dorfman disease
- Destombes-Rosai-Dorfman syndrome

Definitions

- Idiopathic histiocytic proliferative disorder characterized by lymph node-based disease and indolent behavior
 - Extranodal manifestations occur with upper respiratory tract among more common sites of involvement

ETIOLOGY/PATHOGENESIS

Idiopathic

- Etiology remains obscure
- Infectious etiology has been suggested as cause, but infectious agent has never been isolated
 - Discrepancy in literature relative to relationship to Epstein-Barr virus (EBV) and human herpes virus (HHV)
 - Occurrence in patients with rhinoscleroma suggest possible etiological relationship with rhinoscleroma, although this has not been proven
- Other considerations implicated but never substantiated, including
 - Immunodeficiency
 - Autoimmune disease
 - Neoplastic process
- Although some studies implicated SHML as being an IgG4-related disease, it is not believed to belong within spectrum of IgG4-related diseases

Immunophenotype

- Part of mononuclear phagocyte and immunoregulatory effector (M-PIRE) system belonging to macrophage/histiocytic family

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon disease
 - 40% of patients have extranodal disease ± nodal involvement
- Age
 - Occurs over wide range
- Sex
 - Female > male

Site

- Primarily nodal-based proliferation occurring as part of generalized process
- May involve extranodal sites independent of lymph node status
- Head and neck region represents one of more common extranodal areas involved
 - Predilection for
 - Nasal cavity and paranasal sinuses

- Other sites may include orbit/eyelid, gland, cavity (palate), nasopharynx and tonsil, middle ear and temporal bone, larynx, trachea

Presentation

- Symptoms depend on site of occurrence
 - Sinonasal tract symptoms predominantly relate to nasal obstruction
 - Nonsinonasal tract related symptoms may include
 - Mass lesion
 - Pain, stridor, cranial nerve deficits
 - Proptosis, ptosis, decreased visual acuity
- Presentation often includes multiple concurrent sites of involvement
 - May occur with or independent of nodal disease

Laboratory Tests

- Hematologic and immunologic status generally intact
- May be associated with polyclonal elevations in serum protein levels and raised erythrocyte sedimentation rates
- Antineutrophil cytoplasmic antibodies (ANCA) and proteinase 3 (PR3) negative

Treatment

- Options, risks, complications
 - No ideal treatment
 - Treatment protocols mirror clinical manifestations
 - For airway compromise, treatment directed at alleviating obstruction, requiring surgical intervention
 - In patients with extensive or progressive disease, more radical surgical intervention may be required
 - Surgical eradication may prove difficult in cases with involvement of craniofacial bones &/or cranial cavity
- Adjuvant therapy
 - Radiotherapy and chemotherapy utilized, but efficacy not proven

Prognosis

- Considered indolent, self-limiting disease
- Mortality related to SHML is rare
 - Severe morbidity and mortality attributed to complications of SHML
 - Extension of disease to vital structures (e.g., cranial cavity) may rarely result in death
- Unfavorable prognostic factors include
 - Disseminated nodal disease
 - Involvement of multiple extranodal organ systems
 - Deficiencies in hematologic &/or immunologic status

MACROSCOPIC

General Features

- Mucosal thickening or polypoid, nodular, or exophytic growth with rubbery to firm consistency

MICROSCOPIC

Histologic Features

- Submucosal lymphoid aggregates associated with pale-appearing areas composed of histiocytes and plasma cells
 - Lymphocytes and plasma cells are nondescript
 - Plasma cells include intracytoplasmic eosinophilic globules (Russell bodies)

- Lymphoid aggregates composed of mature lymphocytes and histiocytic cells impart mottled appearance
 - True germinal centers are not usually seen
- Histiocytic cells (so-called SHML cells) appear in clusters or cell nests
 - Uniform with mild pleomorphism, round to oval, vesicular to hyperchromatic nuclei, abundant amphophilic to eosinophilic, granular to foamy to clear-appearing cytoplasm
 - Nuclei lack
 - Nuclear lobation
 - Indentation
 - Longitudinal grooving
 - May be obscured by nonhistiocytic cell population (particularly plasma cells)
 - Characteristically demonstrate emperipolesis
 - Phagocytized cells (e.g., lymphocytes, plasma cells, erythrocytes, and polymorphonuclear leukocytes) engulfed within histiocytic cell cytoplasm
 - Tends to be less apparent as compared to nodal-based disease
- Well-formed granulomas and multinucleated giant cells not identified

ANCILLARY TESTS

Cytology

- Cytological features suggesting diagnosis include numerous large benign histiocytes with emperipolesis

Histochemistry

- Special stains for microorganisms negative

Immunohistochemistry

- SHML cells
 - Diffusely S100 protein positive
 - Variably positive
 - CD68 (KP1), MAC387, lysozyme, and α -1-antichymotrypsin (ACT)
 - CD1a and Langerin (CD207) negative
- Plasma cells show kappa and lambda light chain reactivity

DIFFERENTIAL DIAGNOSIS

Infectious (Granulomatous) Diseases

- e.g., rhinoscleroma, leprosy, others
 - Emperipolesis may be present in rhinoscleroma
- Absence of microorganisms

Langerhans Cell Histiocytosis

- Langerhans cells immunoreactive for
 - S100 protein, CD1a, Langerin (CD207)

Granulomatosis With Polyangiitis (Formerly Wegener Granulomatosis)

- Active disease associated with elevations of serum ANCA and PR3
- Histology includes
 - Ischemic-type (geographic) necrosis, vasculitis, scattered multinucleated giant cells
- Mixed inflammatory cell infiltrate, but histiocytes not prominent feature
- Absence of histologic features of SHML

- No immunoreactivity for S100 protein

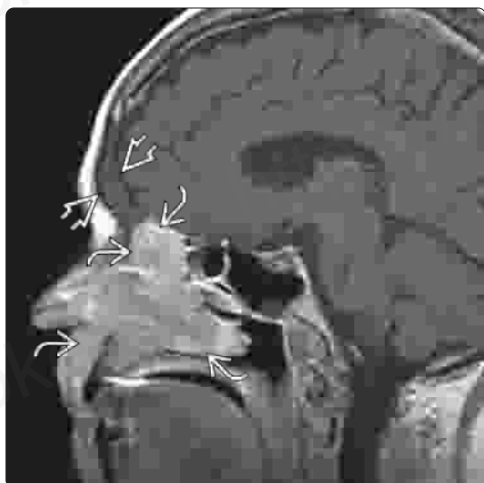
Hematolymphoid Malignancy

- Presence of monomorphic, monoclonal cell population allows for differentiation from SHML
- While rare, emperipolesis can be seen in association with B-cell lymphomas
- SHML on rare occasions has been identified in lymph nodes affected by malignant lymphoma
- Transformation of SHML to high-grade lymphoma reported

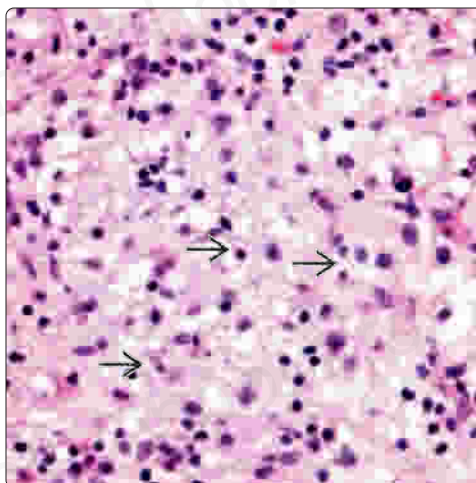
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Imaging of ESHML

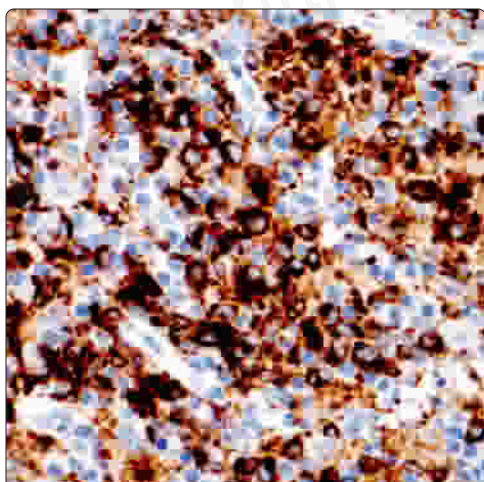


Histiocytic Cells With Admixed Lymphocytes and Plasma Cells

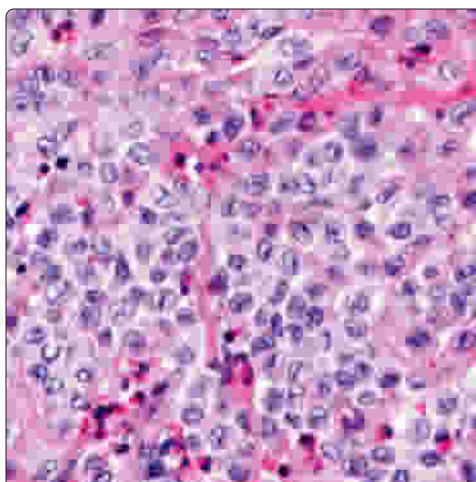


(Left) Sagittal T1WI C+ MR shows enhancing foci of extranodal sinus histiocytosis with massive lymphadenopathy, obstructing the frontal recess and secretions trapped in the frontal sinus. (Right) Readily identifiable histiocytic cells are composed of round nuclei lacking nuclear indentations with abundant lightly eosinophilic cytoplasm with ill-defined borders and scattered admixed mature lymphocytes and plasma cells; emperipolesis is present.

CD68 Immunoreactivity

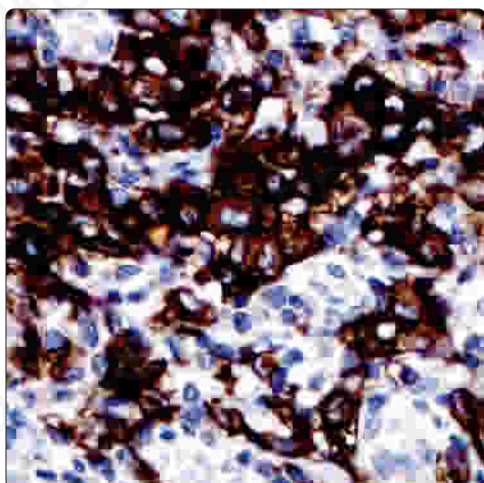


Langerhans Cell Histiocytosis

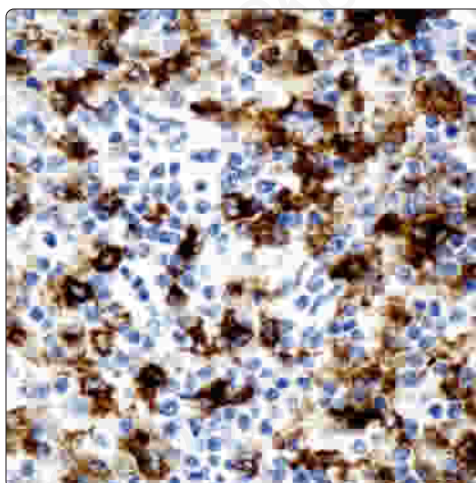


(Left) SHML cells are also reactive with histiocytic markers, including CD68. Other markers that may variably be identified include CD163, HAM56, MAC387, and lysozyme (not shown). (Right) Langerhans cells in Langerhans cell histiocytosis include vesicular nuclei characterized by the presence of lobation of the nuclear membrane lacking emperipolesis. An associated inflammatory cell infiltrate including eosinophils is present.

CD1a Reactivity in Langerhans Cells



Langerin Reactivity in Langerhans Cells



(Left) Like SHML cells, the cells in Langerhans cell histiocytosis are S100 protein positive (not shown). However, in contrast to SHML cells, Langerhans cells are immunoreactive for CD1a. (Right) In addition to the presence of CD1a, Langerhans cells are also immunoreactive for Langerin, further allowing differentiation from extranodal sinus histiocytosis with massive lymphadenopathy.

Myospherulosis

KEY FACTS

TERMINOLOGY

- Innocuous, iatrogenically induced pseudomycotic disease resulting from interaction of red blood cells and petrolatum-based ointments
 - Initially described in Africa where lesions primarily affected subcutaneous tissues or muscle resulting in designation myospherulosis

ETIOLOGY/PATHOGENESIS

- History of surgery prior to development of mass followed by packing of area with petrolatum-based ointment
 - Results from injected or applied medicament acting as foreign substance
 - Origin of myospherules from red blood cells reacting with petrolatum or lanolin found in ointment utilized in packing nasal cavity following surgery
- Emulsified fat may also induce formation of myospherules; thus, fat necrosis may result in myospherulosis

CLINICAL ISSUES

- Nasal cavity and paranasal sinuses among more common sites
- Symptomatic treatment, which may include conservative surgical removal of fibrotic tissues

MICROSCOPIC

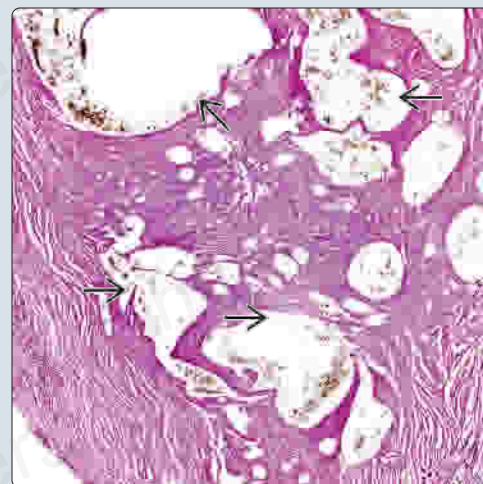
- Pseudocysts (microcysts) embedded within fibrotic tissue creating Swiss cheese appearance
 - Pseudocysts or microcysts measure up to 1 mm in diameter
 - Pseudocysts contain parent bodies
 - Parent bodies contain dark brown endobodies
 - Irregular contour containing round, sac-like structures called parent bodies
 - Spherules or endobodies
 - Usually dark brown
 - Characteristic spherules may be sparse or absent
- Stains for microorganisms negative

Myospherulosis



(Left) Myospherulosis may appear as a polypoid lesion in the sinonasal tract. At low magnification, the lesion polypoid is composed of densely fibrotic tissue within which are several irregularly shaped cystic foci. (Right) Slightly higher magnification shows irregularly shaped pseudocystic spaces embedded in fibrotic tissue containing brown-staining, round, sac-like structures (parent bodies).

Myospherulosis

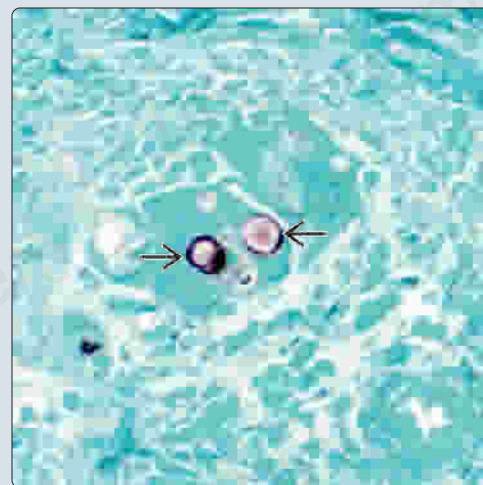


Myospherulosis



(Left) The parent bodies are brown staining and contain numerous spherules or endobodies resembling and potentially confused with microorganisms. However, in contrast to microorganisms, special stains for microorganisms (e.g., GMS, PAS, AFB, others) are negative. (Right) In contrast to the endospores in myospherulosis, the microorganisms in fungal infections as seen in this example of blastomycosis will stain positive by histochemical staining (GMS).

Blastomycosis



TERMINOLOGY

Definitions

- Innocuous, iatrogenically induced pseudomycotic disease resulting from interaction of red blood cells and petrolatum-based ointments
 - Initially described in Africa where lesions primarily affected subcutaneous tissues or muscle resulting in designation myospherulosis

ETIOLOGY/PATHOGENESIS

Iatrogenic

- History of surgery prior to development of mass followed by packing of area with petrolatum-based ointment
- Results from injected or applied medicament acting as foreign substance
 - Origin of myospherules from red blood cells reacting with petrolatum or lanolin found in ointment utilized in packing nasal cavity following surgery
 - Emulsified fat may also induce formation of myospherules; thus, fat necrosis may result in myospherulosis
- Experimental studies show
 - Thin parent body wall of myospherulosis formed initially as result of physical emulsion phenomenon between lipid-containing materials and blood
 - Erythrocytes then enclosed in parent body
 - Parent body membrane gradually reinforced by deposition of plasma proteins, which are insoluble in ethanol
 - Erythrocytes become endobodies by deposition of their contents to membrane of parent body
 - Pores of endobodies formed in process of erythrocyte degeneration
 - Contents of erythrocytes (e.g., hemoglobin) attach to parent body completing myospherulosis

CLINICAL ISSUES

Site

- Nasal cavity and paranasal sinuses among more common sites of involvement
 - Other sites include
 - Ear
 - Soft tissues of extremities

Presentation

- In nose and paranasal sinuses, symptoms generally relate to mass lesion ± airway obstruction
 - Local pain, tenderness may be present
 - May develop from 1 month to years after surgical procedure

Treatment

- Options, risks, complications
 - Prevention using nonpetrolatum-based antibiotic substances
- Surgical approaches
 - Symptomatic treatment that may include conservative surgical removal of fibrotic tissues, which is effective mode of treatment

Prognosis

- Excellent

IMAGING

CT Findings

- Preoperative diagnosis can be suggested on CT of paranasal sinuses by presence of macroscopic paraffin retention cysts with characteristic fat density

MICROSCOPIC

Histologic Features

- Pseudocysts or microcysts are embedded within fibrotic tissue creating Swiss cheese appearance
 - Pseudocysts or microcysts measure up to 1 mm in diameter
 - Irregular contour containing round, sac-like structures called parent bodies
 - Parent bodies measure ~ 50 µm in diameter
 - Parent bodies contain numerous spherules or endobodies
 - Spherules or endobodies
 - Measure ~ 5 µm in diameter
 - Variable in size and shape with cup-shaped forms common
 - Usually dark brown
- Chronic inflammatory infiltrate usually present but may be sparse
 - Composed of lymphocytes, plasma cells, histiocytes, and giant cells
 - Occasional foreign body type multinucleated giant cells may be seen
- Characteristic spherules may be sparse or absent
- Diagnosis can be suggested even in absence of spherules given appropriate history, anatomic location, presence of fibrotic tissue with empty spaces

ANCILLARY TESTS

Histochemistry

- Stains for microorganisms (e.g., GMS, PAS, AFB, Warthin-Starry, others) negative

DIFFERENTIAL DIAGNOSIS

Fungal Infections

- Presence of microorganisms differentiate infectious disease from myospherulosis

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Sinonasal (Schneiderian) Papilloma

KEY FACTS

TERMINOLOGY

- Group of benign epithelial neoplasms arising from sinonasal (schneiderian) mucosa

CLINICAL ISSUES

- Represent < 5% of all sinonasal tract tumors
- Occur over wide age range
- Treatment for all types includes complete surgical excision, including adjacent uninvolved mucosa
 - Tumors recur if incompletely resected

MICROSCOPIC

- Inverted type**
 - Usually lateral nasal cavity (NC) and sinuses; endophytic growth of markedly thickened squamous epithelial proliferation growing downward
 - Thickened squamous epithelial proliferation with admixed mucocytes, intraepithelial mucous cysts
- Exophytic type**

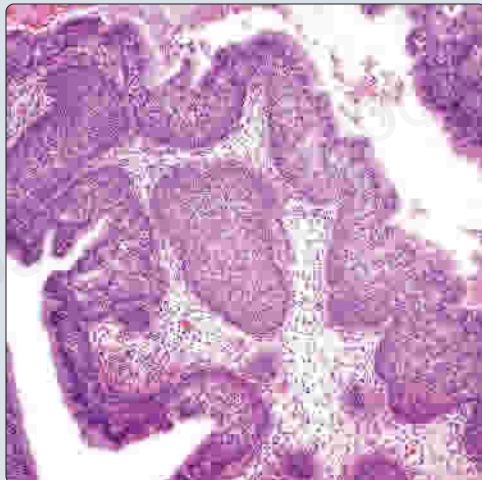
- Exophytic (papillary) growth, usually of septum
- Thickened squamous epithelial proliferation with admixed mucocytes, intraepithelial mucous cysts
- Oncocytic type**
 - Exophytic &/or endophytic growth usually lateral NC and sinuses
 - Multilayered epithelial proliferation composed of columnar cells with abundant eosinophilic and granular cytoplasm
 - Admixed mucocytes (goblet cells) and intraepithelial mucous cysts
- Uncommon malignant transformation: Bone invasion, lack of maturation, disorganization, loss of transepithelial inflammatory infiltrate, increased mitoses (> 25/10 HPF), atypical mitoses, necrosis

TOP DIFFERENTIAL DIAGNOSES

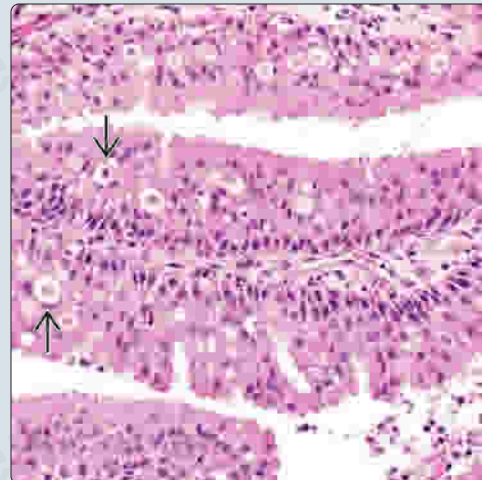
- Sinonasal inflammatory polyps, squamous papilloma (skin), verruca vulgaris (skin), rhinosporidiosis

Schneiderian Papilloma Inverted Type

(Left) There is an inverted growth of the Schneiderian epithelium, showing a tumor in an island within the stroma. There is no destructive infiltration. (Right) Multiple layers of columnar cells with abundant granular to eosinophilic cytoplasm line the papillary projection of this oncocytic-type schneiderian papilloma (SP). Note the intraepithelial mucous cysts with debris.



Schneiderian Papilloma Oncocytic Type



Schneiderian Papilloma Exophytic Type

(Left) Exophytic papilloma shows projections of surface mucosa, composed of a thickened nonkeratinized squamous (epidermoid) epithelium and a fibrovascular stromal core. (Right) All of the SPs will show a variable degree of acute inflammatory cells within the epithelium. It is sometimes referred to as transepithelial elimination of inflammatory cells. Note the small intraepithelial cyst.



Intraepithelial Abscess and Inflammation



TERMINOLOGY

Synonyms

- Sinonasal-type papillomas
- 3 morphologic types identified include
 - Inverted papilloma (IP)
 - Exophytic (fungiform, septal)
 - Oncocytic (cylindrical or columnar cell)

Definitions

- Group of benign epithelial neoplasms arising from sinonasal (schneiderian) mucosa

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Human papillomavirus (HPV)
 - Found in septal and inverted papillomas by in situ hybridization or PCR
 - ~ 25% by in situ hybridization, consensus PCR, and type-specific PCR
 - Subtypes 6/11 > 16/18 (2.8:1 ratio); rarely other HPV subtypes (e.g., HPV 57)
 - HPV detection rates are higher in inverted papilloma with high-grade dysplasia or carcinoma (~ 55%)
 - Ratio of low-risk:high-risk HPV shifts from benign to malignant
 - Low risk:high risk 4.8:1 (benign) to 1:2.4 (carcinoma)
 - Presence of HPV is significantly associated with likelihood of recurrence (odds ratio [OR]: 10.2)
 - Molecular biologic analysis to date on oncocytic papillomas has not identified presence of HPV
- Discrepant reports on presence of Epstein-Barr virus in schneiderian papillomas

CLINICAL ISSUES

Epidemiology

- Incidence
 - Represent < 5% of all sinonasal tract tumors
 - Inverted type is more common although literature states septal type is most common
 - Oncocytic type is least common
- Age
 - Occur over wide age range
 - Rare in children
 - **Inverted type**
 - Most common in 5th-8th decades
 - **Exophytic type**
 - Tend to occur in younger age group
 - **Oncocytic type**
 - Tend to occur in older age range (> 50 years)
 - Uncommon under 4th decade of life

Site

- **Inverted type**
 - Occurs in maxillary sinus (42%) and ethmoid sinus/recess (18%)
 - Nasal cavity (15%) and turbinates (12%) frequently affected
 - Less often extends/involves frontal (10%), sphenoid (2%), and ethmoid (2%) sinuses

- May occur in paranasal sinus without involvement of nasal cavity

- **Exophytic type**
 - Almost invariably limited to nasal septum
- **Oncocytic type**
 - Most often occurs along lateral nasal wall
 - May originate within paranasal sinus (maxillary or ethmoid)
- Inverted and oncocytic types rarely occur on nasal septum
- Typically, schneiderian papillomas are unilateral
 - Bilateral papillomas, particularly inverted type, may occur in up to 10%
 - In presence of bilateral disease, clinical evaluation indicated to exclude extension from unilateral disease (i.e., septal perforation)
- Schneiderian-type papillomas may originate in nasopharynx or middle ear (eustachian tube) without connection to sinonasal tract
 - Probably arise from misplaced ectodermal-derived epithelial rests from sinonasal tract

Presentation

- Symptoms vary according to site of occurrence
 - Airway obstruction, asymptomatic mass, epistaxis, discharge, sinusitis, pain

Treatment

- Surgical approaches
 - Treatment for all sinonasal papillomas includes complete surgical excision, including adjacent uninvolved mucosa
 - Growth and extension along mucosa result from induction of squamous metaplasia in adjacent sinonasal mucosa, necessitating excision of adjacent mucosa
 - Adequate surgery includes lateral rhinotomy or medial maxillectomy with en bloc excision
 - Functional endoscopic sinus surgery may be employed with good results
- Adjuvant therapy
 - Radiation may prove beneficial in select population of patients with unresectable tumors due to locally advanced disease

Prognosis

- Good following complete surgical excision
- Complications
 - Tumors recur if incompletely resected
 - Recurrence probably represents persistence of disease rather than multicentricity of neoplasm
 - If left unchecked, capability of continued growth with extension along mucosal surface with invasion/destruction of vital structures
- Limited but real risk of malignant transformation: 2-4% for inverted and oncocytic types; < 1% for exophytic type

IMAGING

General Features

- Appearance varies with extent of disease
 - Soft tissue density seen early in disease
 - Opacification, mucosal thickening present with more extensive disease

Sinonasal (Schneiderian) Papilloma

- Evidence of pressure erosion of bone may be seen

MACROSCOPIC

General Features

- **Inverted type**
 - Large, bulky, translucent masses with red to gray color, varying from firm to friable in consistency
- **Exophytic type**
 - Papillary, exophytic, verrucoid lesion with pink to tan appearance, firm to rubbery consistency; often attached to mucosa by narrow or broad-based stalk
- **Oncocytic type**
 - Dark red to brown, papillary or polypoid lesions

MICROSCOPIC

Histologic Features

- **Inverted type**
 - Endophytic or inverted growth pattern consisting of markedly thickened squamous epithelial proliferation growing downward
 - Epithelium varies in cellularity composed of squamous, transitional, and columnar cells (all 3 may be present in given lesion) with admixed mucocytes (goblet cells) and intraepithelial mucous cysts
 - Cells generally bland in appearance with uniform nuclei, no piling up, but mild pleomorphism may be present
 - Mitotic figures may be seen in basal and parabasal layers, but atypical mitotic figures are not identified
 - Epithelial cells may demonstrate extensive clear cell features indicative of abundant glycogen content
 - Mixed inflammatory cell infiltrate characteristically seen within all layers of surface epithelium
 - Stromal component varies from myxoid to fibrous with admixed chronic inflammatory cells and variable vascularity
 - May occur simultaneously with nasal inflammatory polyps
 - Surface keratinization may be present
- **Exophytic type**
 - Papillary fronds composed of thick epithelium, which is predominantly squamous (epidermoid) and, less frequently, respiratory type
 - Mucocytes (goblet cells) and intraepithelial mucous cysts are present
 - Surface keratinization is uncommon
 - Stromal component is composed of delicate fibrovascular cores
- **Oncocytic type**
 - Exophytic &/or endophytic (inverted) growth
 - Multilayered epithelial proliferation composed of columnar cells with abundant eosinophilic and granular cytoplasm
 - Nuclei vary from vesicular to hyperchromatic; nucleoli are usually indistinct
 - Often "tram-tracked": Basal and luminal parallel lining up of nuclei
 - Outer surface of epithelial proliferation may demonstrate cilia
 - Intraepithelial mucinous cysts, often containing neutrophils
 - Cysts are not identified in submucosa
 - Stromal component varies from myxoid to fibrous with admixed chronic inflammatory cells and variable vascularity
 - May occur simultaneously with nasal inflammatory polyps
- **Malignant transformation**
 - Incidence of malignant transformation varies per subtype
 - Inverted type: ~ 2%
 - Oncocytic type: ~ 4%
 - Exophytic type rarely, if ever
 - Majority of malignancies are keratinizing squamous cell carcinoma (SCC); less frequently nonkeratinizing SCC
 - Other carcinomas may rarely occur, including
 - Verrucous carcinoma, mucoepidermoid carcinoma, small cell carcinoma, adenocarcinoma, and undifferentiated carcinoma
 - Carcinoma may occur synchronously or metachronously with papilloma (most seen synchronous)
 - Carcinomatous foci may be limited or extensive, may show epithelial dysplasia/carcinoma in situ or invasive carcinoma
 - Evidence of preexisting papilloma
 - May be present with obvious transition from benign papilloma to overt carcinoma
 - May include predominantly benign tumor (papilloma) with limited foci of carcinoma
 - May predominantly include carcinoma with limited residual papilloma
 - May be no residual evidence of preexisting benign tumor; known to have prior papilloma by history only
 - No reliable histologic features predict which papillomas likely to **become** malignant
 - No correlation between number of recurrences and development of carcinoma
 - Histologic features of malignancy include bone invasion, lack of maturation, disorganization, loss of transepithelial inflammatory infiltrate, increased mitoses (> 25/10 HPF), atypical mitoses, necrosis
 - Treatment for malignant transformation includes surgery and radiotherapy
 - Prognosis for patients with malignant transformation varies
 - Carcinoma only locally invasive associated with favorable prognosis following treatment
 - Carcinoma extensively invasive with involvement of vital structures &/or metastatic disease associated with poor outcome
 - Prognosis similar to de novo sinonasal squamous carcinoma

ANCILLARY TESTS

Histochemistry

- Mucicarmine: Intracytoplasmic mucin-positive material in goblet cells
- Periodic acid-Schiff with diastase: Intracytoplasmic mucinous material

Sinonasal (Schneiderian) Papillomas			
	Inverted Type	Exophytic Type	Oncocytic Type
Incidence	47-73%	20-50%	3-8%
Gender	M > F	M > F	M = F
Age	40-70 years	20-50 years	> 50 years
Location	Lateral nasal wall in region of middle turbinates; may extend into sinuses (maxillary or ethmoid)	Nasal septum	Lateral nasal wall and sinuses (maxillary or ethmoid)
Focality	Typically unilateral; rarely bilateral	Unilateral	Unilateral
Histology	Endophytic or inverted growth composed predominantly of squamous (epidermoid) cells with scattered admixed mucocytes and intraepithelial mucous cysts; mixed chronic inflammatory cell infiltrate characteristically seen within all layers of surface epithelium	Exophytic to papillary proliferation composed predominantly of squamous (epidermoid) epithelium with admixed mucocytes and intraepithelial mucous cysts; delicate fibrovascular cores	Multilayered epithelial proliferation composed of columnar cells with abundant eosinophilic and granular cytoplasm; outer surface of epithelial proliferation may demonstrate cilia; intraepithelial mucous cysts, often containing polymorphonuclear leukocytes
Association with HPV	~ 38% positive; HPV 6 and HPV 11; less frequently HPV 16, HPV 18; rarely HPV 57	~ 50% positive; HPV 6 and HPV 11; less frequently HPV 16, HPV 18; rarely HPV 57	Typically absent
Malignant transformation	~ 2%; most common type is keratinizing SCC, then MEC	Rare	~ 4%; most common type is keratinizing SCC

HPV = human papillomavirus; SCC = squamous cell carcinoma; MEC = mucoepidermoid carcinoma.

Immunohistochemistry

- HPV DNA seen in IP with high prevalence but limited transcriptional activity
- Strong positive: p63, p16, p21, p27, pRb, cyclin D1
- p53, p21, and p27 show increased intensity and altered distribution in dysplasia and carcinoma
- Ki-67 labeling index > 20% and above basal zone usually seen in dysplasia and carcinoma

Genetic Testing

- Inverted papillomas shown to be monoclonal proliferations but, unlike squamous epithelial dysplasia, do not harbor key genetic alterations associated with malignant transformation
- *TP53* gene mutation appears closely associated with malignant transformation in sinonasal papillomas

DIFFERENTIAL DIAGNOSIS

Sinonasal Inflammatory Polyps

- Often coexist with schneiderian papillomas but lack epithelial proliferation with constituent cells of schneiderian papillomas

Squamous Papilloma of Nasal Vestibular Skin

- Cutaneous lesion entirely comprised of squamous cells without identifiable intraepithelial mucocytes
- Staining for epithelial mucin (mucicarmine, diastase PAS) helpful in differential diagnosis

Verruca Vulgaris of Nasal Vestibular Skin

- Characteristic findings include prominent keratinization with verrucoid or papillomatous growth, keratohyaline granules, koilocytes, and inturning of rete pegs
- Absence of intraepithelial mucocytes

Rhinosporidiosis

- Specific differential diagnosis with oncocytic-type papilloma
- Usually **submucosal** sporangia containing microorganisms

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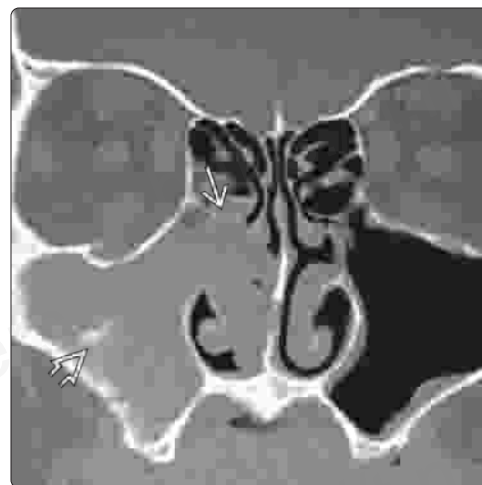
Sinonasal (Schneiderian) Papilloma

Computed Tomography of Schneiderian Papilloma

(Left) CT scan demonstrates a large mass filling the lateral wall of the nasal cavity and expanding into the sinuses. This particular finding is nonspecific but does raise a polyp or papilloma in the differential diagnosis. (Right) Coronal bone CT shows a lobular inverted papilloma centered at the middle meatus. The lesion enters the maxillary sinus via an enlarged infundibulum and is partially calcified.

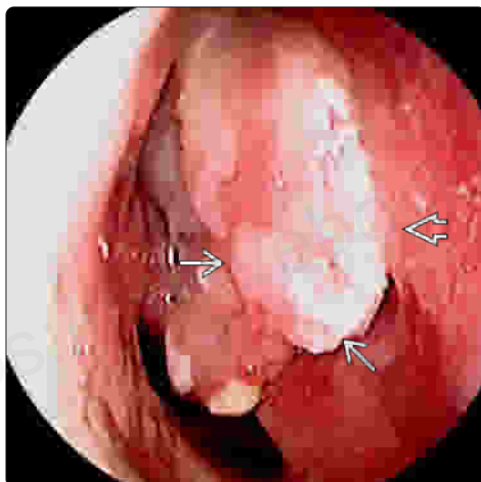


Maxillary Sinus and Nasal Cavity Mass

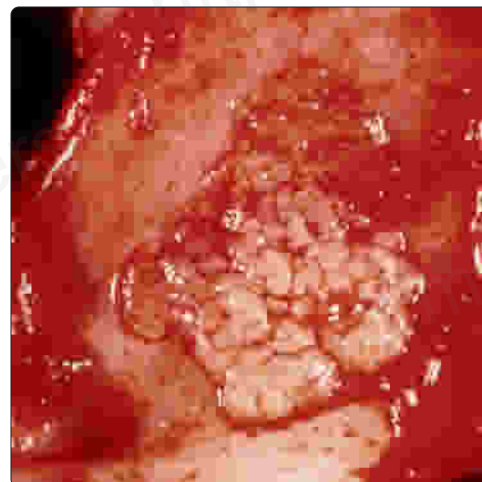


Endoscopic View of Inverted Papilloma

(Left) Endoscopic photograph during nasal endoscopy of an inverted papilloma shows a pale, lobular mass at the middle meatus. The lesion abuts the nasal septum medially. (Right) This gross photograph shows a cerebriform appearance to an SP. This type of multiple papillary projections is most helpful in the diagnosis of this type of papilloma.



Cerebriform Appearance of Schneiderian Papilloma

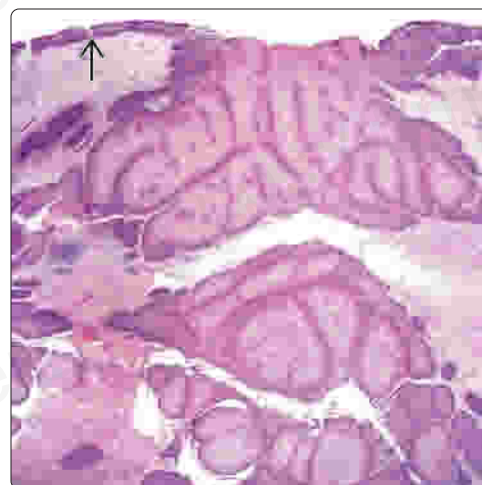


Inverted Pattern of Growth

(Left) Endophytic or inverted growth pattern consists of thickened epithelial nests arising from the surface respiratory epithelium with downward growth. The nests may not be very deep. (Right) Multiple inverted projections are seen deep within the stroma below an intact surface epithelium. The nests all show a well-defined border, helping to exclude an invasive neoplasm.



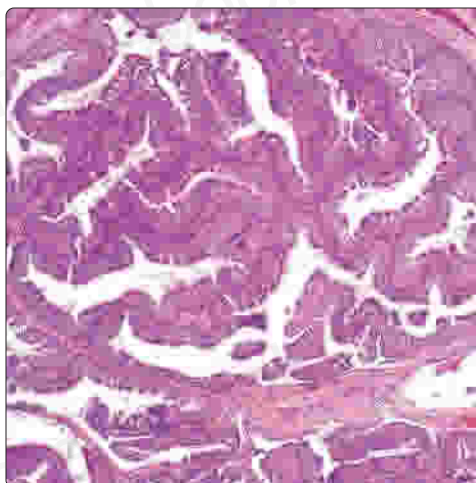
Inverted Projections Below Surface



Papillary Projections of Inverted Schneiderian Papilloma

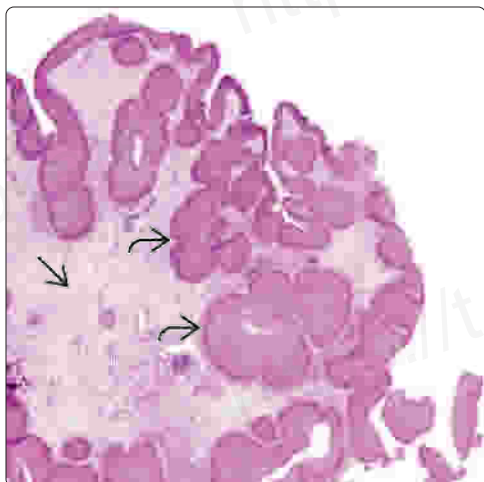


Broad Pushing Inversions of Schneiderian Papilloma

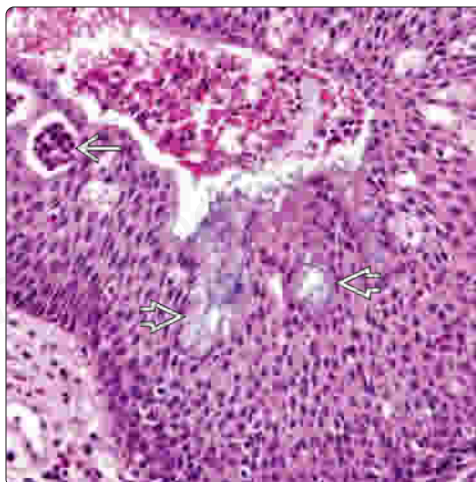


(Left) Multiple papillary projections are seen in this tumor, which is an example of an inverted-type SP. There is an inverted growth of the proliferation into the stroma, even though there is an exophytic overall projection. (Right) Multiple inverted projections are noted. There is a general complexity to this proliferation, as it shows a broad, pushing border with the surrounding stroma.

Endophytic Projections Into Stroma

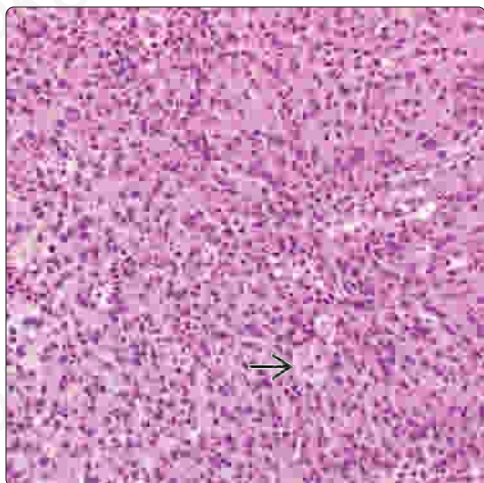


Mucocytes and Microabscesses

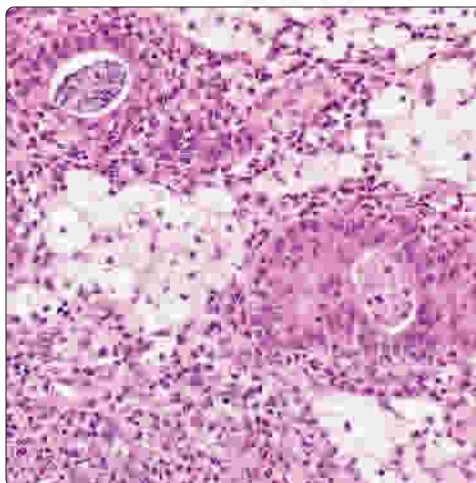


(Left) Endophytic or inverted growth pattern of thickened epithelial nests arising from surface epithelium is characteristic of inverted-type papilloma. Stroma shows alterations similar to those seen in inflammatory polyps. (Right) This tumor shows multiple mucocytes at the surface and within the proliferation. There are also microabscesses of inflammatory cells within the epithelium, another feature seen in SP.

Numerous Inflammatory Cells



Stromal Histiocytes



(Left) There are innumerable acute inflammatory cells (neutrophils and eosinophils) in this epithelium that is part of an SP. Small cysts are noted. (Right) SP may have stromal foamy histiocytes present, along with the areas of inflammatory cells. This is a nonspecific finding.

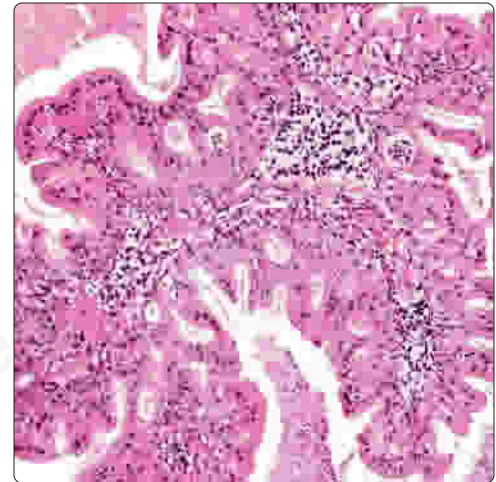
Sinonasal (Schneiderian) Papilloma

(Left) SP, oncocytic type, shows an epithelial proliferation with exophytic/papillary and focally endophytic growth. The stroma shows edematous changes similar to that of sinonasal polyps. **(Right)** There is a very rich oncocytic appearance to the epithelium in this oncocytic SP. There is a uniformity to the cells as the columnar epithelial cells are expanded to the surface. Cilia are easily noted.

Papillary Projections of Oncocytic Schneiderian Papilloma

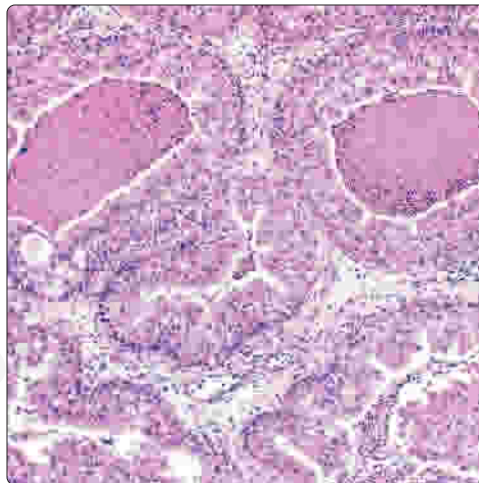


Papillary Projections of Oncocytic Epithelium

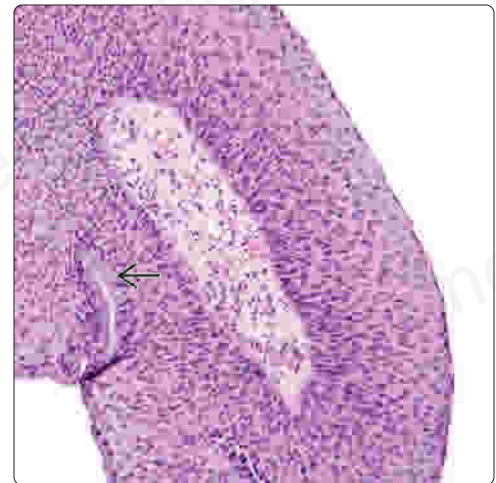


(Left) It is not uncommon to see areas of degeneration or debris within the center of epithelial islands of SP. In this case, it is an oncocytic SP with layered nuclei in the epithelium and central areas of degeneration. **(Right)** At high magnification, the nonkeratinizing squamous epithelium shows cytomorphic uniformity with cellular maturation, retention of cellular polarity, and absence of cytologic atypia. Focally, scattered mucocytes are present.

Degeneration Within Oncocytic Epithelium



Exophytic-Type Schneiderian Papilloma

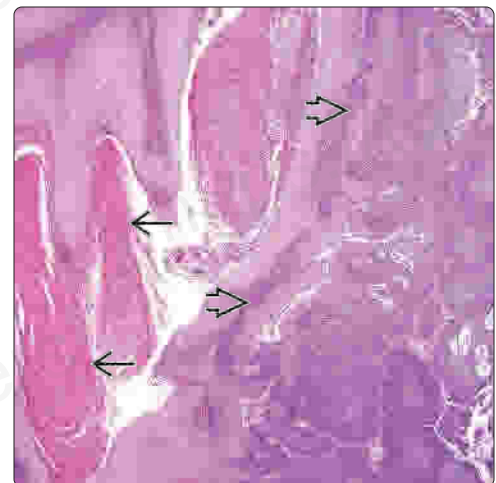


Focal Mucocytes in Exophytic Schneiderian Papilloma

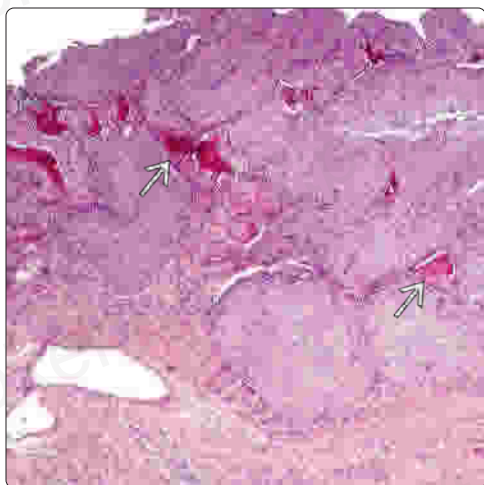


(Left) Exophytic papilloma, with the most superficial aspect retaining respiratory epithelial mucocytes, is otherwise replaced by benign-appearing squamous (epidermoid) epithelium. **(Right)** This exophytic papilloma shows increased keratinization, while the right side of the image shows a transformation into a carcinoma. In this case, it is a squamous cell carcinoma, the most common type identified.

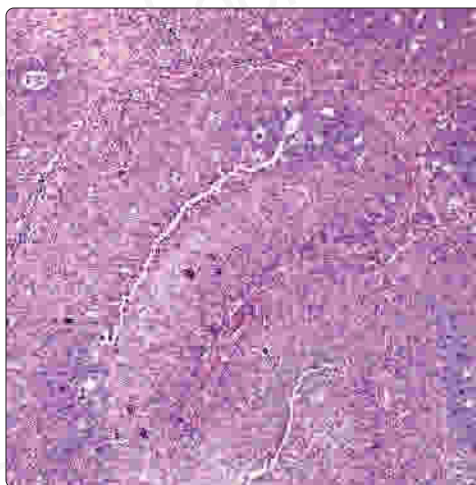
Transition to Squamous Cell Carcinoma



Bone Destruction by Malignant Schneiderian Papilloma

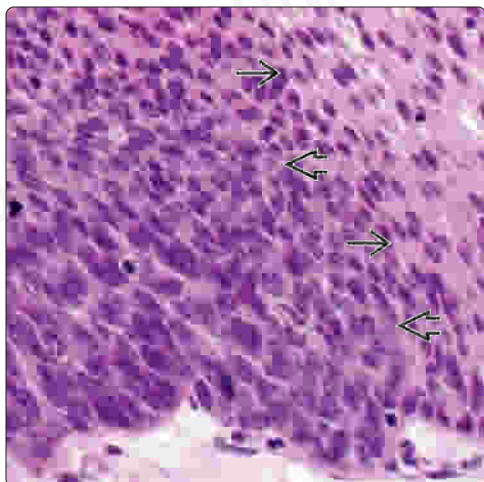


Malignant Transformation of Schneiderian Papilloma

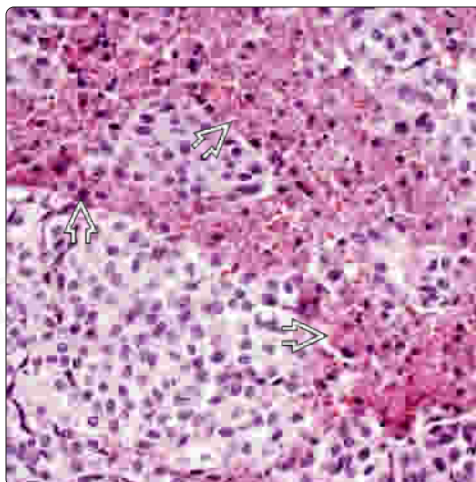


(Left) There is expansion of this tumor into the bone with destructive growth into the deep stroma. This is a tumor that has undergone malignant transformation into carcinoma. (Right) There is a loss of polarity with marked increased in cellularity in this area of malignant transformation of an SP. Pleomorphism is easily identified with increased mitoses although there are still many acute inflammatory cells present.

Transition From Benign to Malignant

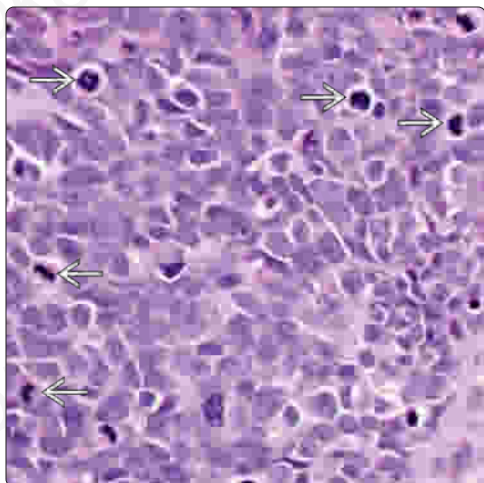


Comedo-Type Necrosis

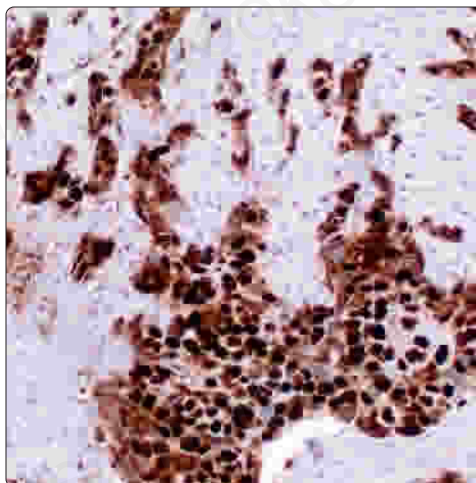


(Left) There is an area of transition from the benign epithelium into the area of malignant epithelium of an SP with malignant transformation. Note the increased cellularity and increased number of mitoses. (Right) Genuine, comedo-type necrosis is a feature seen in malignant transformation of SP. This is not a degenerative-type necrosis but a true tumor necrosis.

Remarkably Increased Mitoses



p53 in Area of Carcinoma



(Left) While mitoses can be seen in papilloma, the remarkable number seen in this tumor are beyond what would be seen in a benign lesion and are a tip-off to the diagnosis of carcinoma. This is an example of squamous cell carcinoma. (Right) There is frequently a gradient of p53 immunoreactivity in SP. Usually, the basal zone shows reactivity with p53, but, in carcinoma (as shown), there is strong and diffuse, nearly full-thickness reactivity.

KEY FACTS

TERMINOLOGY

- Benign, epithelial-derived neoplasm with epithelial and myoepithelial differentiation

CLINICAL ISSUES

- Rare, although comprises ~ 25% of all sinonasal tract **glandular** neoplasms
- Usually between 20-60 years; mean: 40 years
- Female > male (1.1:1)
- Mucosa of bony or cartilaginous nasal septum is most commonly affected
- Local, but complete, surgical excision to prevent recurrence/residual disease
- Excellent, although recurrence (< 8%) usually related to incomplete excision

MACROSCOPIC

- Mucosa-covered, firm, pedunculated, polypoid or sessile, broad-based, fleshy mass

- Usually small: Range: 0.5-5 cm; mean: 2.5 cm

MICROSCOPIC

- Unencapsulated but usually circumscribed tumors
- Tumors are highly cellular and solid, with scant chondromyxoid matrix
- Epithelial elements revealed with admixture of well-formed, although rare tubuloductal structures
- Myxohyaline or cartilaginous stroma focally
- Mitotic figures seen, but not increased nor atypical

ANCILLARY TESTS

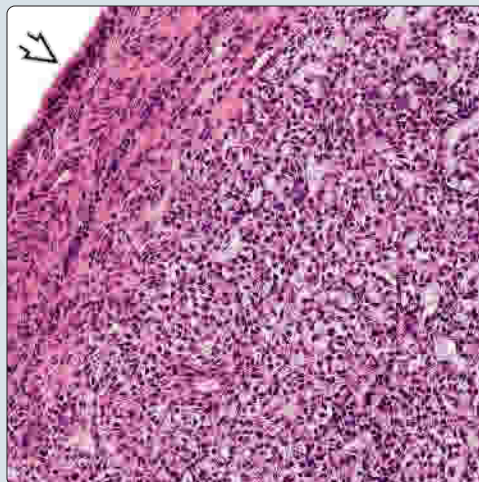
- Biphenotypic **positive**: pancytokeratins, GFAP, S100 protein, SOX10, actins, calponin, p63

TOP DIFFERENTIAL DIAGNOSES

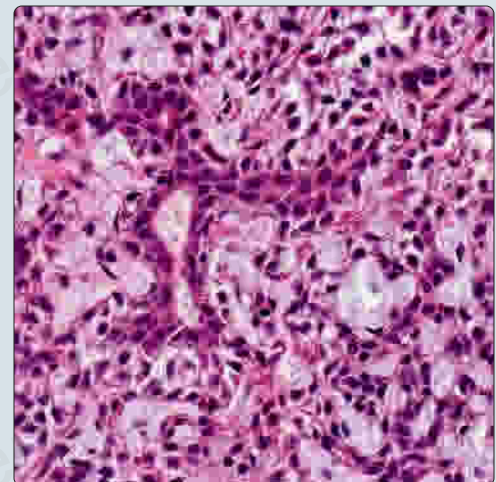
- Basal cell adenoma, adenoid cystic carcinoma, polymorphous low grade adenocarcinoma, sinonasal adenocarcinoma nonintestinal type, chondroid syringoma

(Left) Hematoxylin and eosin shows an intact respiratory epithelium overlying a cellular pleomorphic adenoma with a predominantly glandular pattern. (Right) Hematoxylin and eosin shows myxoid matrix material with associated epithelial neoplasm. The epithelium shows gland-duct formation as well as ribbons and strips of epithelium.

Intact Mucosa With Cellular PA

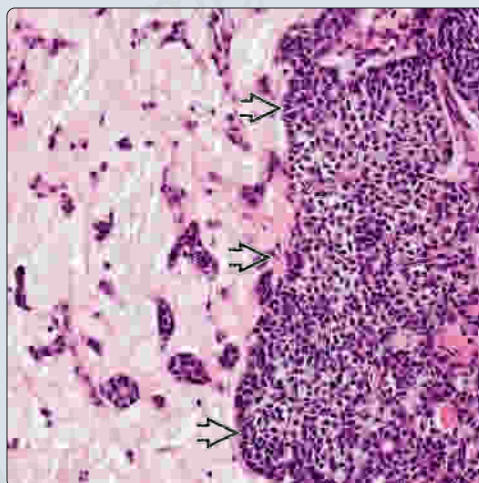


Stromal Chondromyxoid Matrix Material

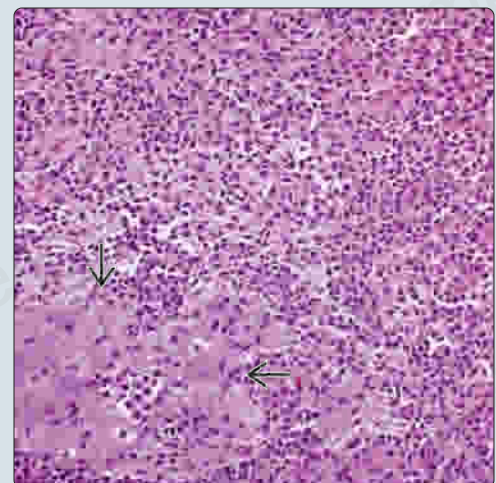


(Left) Hematoxylin and eosin demonstrates the abrupt juxtaposition between the cellular and chondromyxoid matrix compartments of this pleomorphic adenoma. Sampling would be important in this tumor type. (Right) The neoplastic cells in a pleomorphic adenoma, especially in minor salivary gland locations, are often more plasmacytoid than other sites, as seen here. Note the chondroidmyxoid stroma.

Juxtaposition of Cellular Compartments



Plasmacytoid Population



TERMINOLOGY

Abbreviations

- Pleomorphic adenoma (PA)

Synonyms

- Benign mixed tumor (BMT), intranasal mixed tumor, nasal blastoma, mixed salivary tumor, chondroid syringoma

Definitions

- Benign, epithelial-derived neoplasm whose cells demonstrate both epithelial and myoepithelial differentiation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare, although comprises ~ 25% of all sinonasal tract glandular neoplasms
- Age
 - Usually between 20 and 60 years; mean: 40 years
- Sex
 - Female > male (1.1:1)

Site

- Mucosa of bony or cartilaginous nasal septum is most commonly affected
- Nasal turbinates next most common site affected, where it may extend into maxillary sinus(es)

Presentation

- Nonspecific signs and symptoms
 - Unilateral obstruction, mass, epistaxis
 - Congestion, difficulty breathing, discharge

Treatment

- Local, but complete, surgical excision to prevent recurrence/residual disease
 - Various surgical approaches: Endoscopic endonasal surgery, lateral rhinotomy, midfacial degloving, and transpalatal surgery

Prognosis

- Excellent, although recurrence (< 8%) usually related to incomplete excision
- Rare, malignant transformation can be seen (usually adenoid cystic carcinoma)

IMAGING

Radiographic Findings

- Few studies, but MR shows mass with low signal intensity on T1-weighted images and heterogeneous, intermediate signal intensity on T2-weighted images
- Generally, bone remodeling or resorption, not destruction

MACROSCOPIC

General Features

- Mucosa-covered, firm, pedunculated, polypoid or sessile, broad-based, fleshy mass
- Usually arising from septum

Size

- Usually small: Range: 0.5-5 cm; mean: 2.5 cm

MICROSCOPIC

Histologic Features

- Unencapsulated but usually circumscribed tumors
- Tumors are highly cellular and solid, with scant myxochondroid matrix
- Myoepithelial cells with plasmacytoid appearance usually predominate
- Epithelial elements revealed with admixture of well-formed, although rare tubuloductal structures
- Myoepithelial cells can be spindled, round, stellate, and polygonal
- Myxohyaline or cartilaginous stroma focally
- Cellular pleomorphism is limited
- Mitotic figures seen, but not increased nor atypical
- Rarely, carcinoma ex pleomorphic adenoma may develop

ANCILLARY TESTS

Immunohistochemistry

- Biphenotypic **positive**: Pancytokeratins, GFAP, S100 protein, SOX10, actins, calponin, p63

DIFFERENTIAL DIAGNOSIS

Basal Cell Adenoma

- Basal cells without plasmacytoid features; no myxoid matrix

Adenoid Cystic Carcinoma

- Infiltrative, destructive growth; cribriform; peg-shaped cells; increased mitotic activity; perineural invasion

Polymorphous Low-Grade Adenocarcinoma

- Infiltrative; perineural invasion; vesicular open nuclear chromatin; limited mitoses; lacks chondroid matrix

Nonintestinal Sinonasal Adenocarcinoma

- Tubulo-glandular neoplasm; destructive growth; mitotic figures; pleomorphism

Chondroid Syringoma

- Skin based lesion, but may expand into nasal cavity

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KEY FACTS

TERMINOLOGY

- Benign pituitary gland neoplasm occurring separately from, and without involvement of, sella turcica (normal anterior pituitary gland)

CLINICAL ISSUES

- Presents with space-occupying effects or endocrine abnormalities (~ 40%)
 - Sphenoid sinus > > cavernous sinus
- Mean age: 54 years
- Female > male (1.3:1)
- Complete surgical removal, followed by medical/hormone manipulation

IMAGING

- Intrasphenoidal mass with erosion of sellar floor seen best with thin-section MR or CT

MICROSCOPIC

- Submucosal location of unencapsulated tumor

- Invasion into bone is frequently seen, but **no** perineural or lymphovascular invasion
- Tumors arranged in many patterns, separated by delicate fibrovascular septa
 - Solid, organoid, rosettes/pseudorosettes, single file, glandular, trabecular, insular
- Variety of cell types can be seen, including polygonal, plasmacytoid, granular, oncocytic, cuboidal, and spindled
- Necrosis is seen in ~ 25% of cases

ANCILLARY TESTS

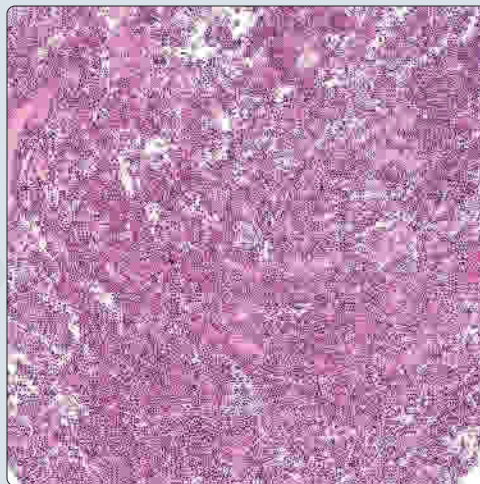
- Epithelial **(+)**: Cytokeratin, CAM5.2; **negative**: CK7, CK5/6
- Neuroendocrine **(+)**: Synaptophysin, chromogranin, CD56
- Hormone peptides: Prolactin (60%) most common

TOP DIFFERENTIAL DIAGNOSES

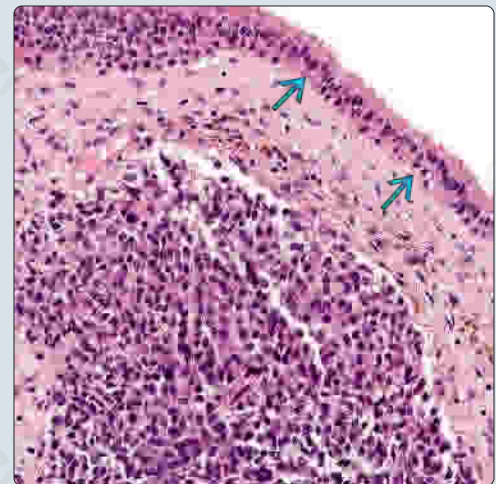
- Olfactory neuroblastoma, Ewing sarcoma/PNET, neuroendocrine carcinoma, meningioma, melanoma, squamous cell carcinoma, lymphoma

Sheets of Neoplastic Cells

(Left) There are sheets of neoplastic cells arranged in a solid to focally trabecular architecture. Delicate fibrovascular septa are noted throughout. **(Right)** There is a submucosal location to this unencapsulated ectopic pituitary adenoma. The surface epithelium is intact and uninvolved by the tumor, showing a well-developed grenz zone of separation.

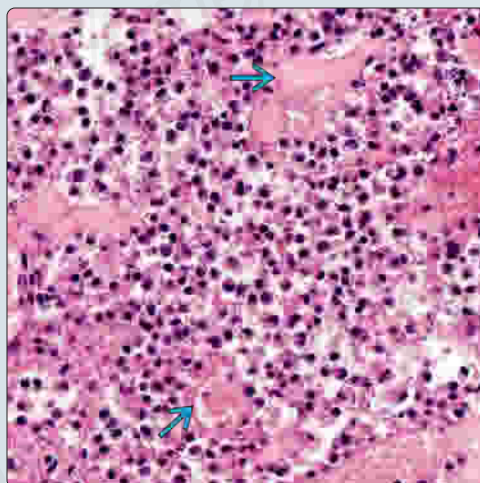


Tumor Below Intact Surface Epithelium

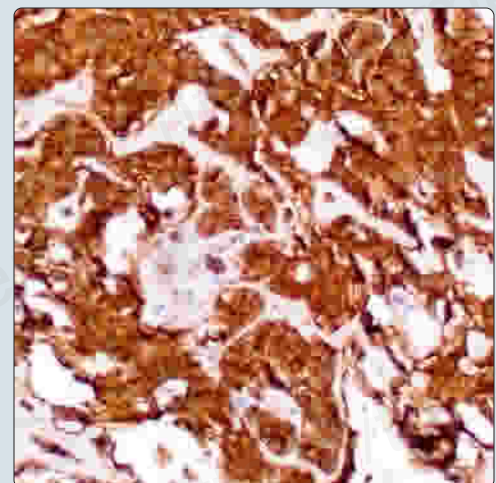


Monotonous Neoplastic Proliferation

(Left) This very cellular tumor shows solid to vaguely trabecular architecture, separated by delicate fibrovascular septa. The neoplastic population is monotonous, showing eccentrically located, round nuclei. **(Right)** If the type of tumor is uncertain, none of the tumors in the differential diagnosis react with specific peptides, which can also be secreted in the serum. This tumor shows a strong and diffuse cytoplasmic prolactin reaction.



Strong Cytoplasmic Prolactin Reaction



TERMINOLOGY

Definitions

- Benign pituitary gland neoplasm occurring separately from, and without involvement of, sella turcica (normal anterior pituitary gland)
 - Direct extension from intrasellar neoplasm is much more common (seen in ~ 2% of pituitary tumors) and must be excluded

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Anterior pituitary primordium appears at ~ 4 weeks of embryogenesis
- During 8th developmental week, pituitary divides into sellar and pharyngeal parts
 - Supradiaphragmatic attachment to pituitary stalk
 - Cephalic invagination of Rathke pouch (intrasellar)
- Migration into sphenoid or pharynx can be seen, often along craniopharyngeal canal
 - Ectopic pituitary adenomas are thought to be derived from these embryologic remnants along migration path of Rathke pouch
 - Leptomeningeal locations are common but still intracranial
- Fully functional tissue in these ectopic locations is compatible with normal life
 - Pharyngeal pituitary begins hormone function at 17th-18th week, up to 8 weeks after sellar pituitary

CLINICAL ISSUES

Epidemiology

- Incidence
 - Pituitary adenomas account for 10-15% of intracranial neoplasms
 - Rare in ectopic locations within upper aerodigestive tract
- Age
 - Wide range: 2-84 years
 - Mean: 54 years
- Sex
 - Female > male (1.3:1)

Site

- Sphenoid sinus >>> cavernous sinus > 3rd ventricle > nasopharynx, nasal cavity, clivus >> petrous temporal bone
 - Must exclude invasive sellar tumors or direct extension from intracranial primary
 - Intact pituitary sella is usually required

Presentation

- Space-occupying effects
 - Nasal obstruction, sinusitis, rhinorrhea, discharge or drainage
 - Headache and pain (cranial nerve[s] paralysis)
 - Visual disturbances (diplopia, acuity loss, blurring)
 - Asymptomatic
- Endocrine abnormalities seen in ~ 40% of patients
 - Cushing disease (adrenocorticotrophic hormone [ACTH]) most common
 - Bruising, hypertension, acne, facial hair, weakness

- Acromegaly (growth hormone [GH])
- Hyperthyroidism (thyroid-stimulating hormone [TSH])
- Amenorrhea, hirsutism, impotence (prolactin [PRL])
- Diagnosis unsuspected in functionally silent tumors

Laboratory Tests

- All ectopic hormones can be measured serologically or via stimulation/suppression testing
 - ACTH, GH, TSH, prolactin, cortisol
 - Releasing hormones can also be measured

Treatment

- Surgical approaches
 - Complete surgical removal
- Drugs
 - Medical/hormonal manipulation
 - Dopamine-agonists (bromocriptine), somatostatin analogs (octreotide), corticosteroids (hydrocortisone, prednisone), thyroxine
- Radiation
 - Stereotactic radioablation, usually for larger or incompletely removed tumors

Prognosis

- Excellent prognosis with control of endocrine abnormalities after complete surgical resection
 - Morbidity associated with hormonal manifestations and local invasion (bone or cranial cavity extension)
- Recurrence/persistence may be seen in large tumors

IMAGING

Radiographic Findings

- Thin-section MR (± contrast) or CT yields best results
- Intrasphenoidal mass with erosion but usually not expansion of sellar floor
- Usually show early, intense, but heterogeneous enhancement
- CT and MR define extent and location of tumor

MACROSCOPIC

General Features

- Polypoid and pedunculated mass
- Solitary mass

Size

- Mean: 2.9 cm; range: 0.5-8.0 cm
- Tumor size does not seem to correlate with symptom severity

MICROSCOPIC

Histologic Features

- Submucosal location of unencapsulated tumor
 - Surface epithelium is intact and uninvolved
- Invasion into bone and soft tissue is frequently seen, but there is **no** perineural or lymphovascular invasion
- Tumors arranged in many patterns
 - Solid, organoid, rosettes/pseudorosettes, single file, papillary, glandular, trabecular, insular
- Tumor groups separated by delicate fibrovascular septa

- Extracellular stromal hyalinization or sclerosis may be seen
- Hemorrhage is frequently seen in background
- Secretions or concretions can be seen
- Necrosis is seen in ~ 25% of cases
- Variety of cell types can be seen, including polygonal, plasmacytoid, granular, oncocyctic, cuboidal, and spindled
- Monotonous population of epithelial cells
 - Round or oval nuclei with "salt and pepper," clumped chromatin
 - Inconspicuous or small nucleoli
 - Eosinophilic, amphophilic or clear, eccentrically located cytoplasm
 - Intracellular cytoplasmic inclusions commonly present
- Isolated nuclear pleomorphism and multinucleated tumor cells are common
- Mitoses are usually limited (0-3/10 HPFs, range)

ANCILLARY TESTS

Immunohistochemistry

- Epithelial **positive**: Cytokeratin, CAM5.2
 - **Negative**: CK7, CK5/6
- Neuroendocrine markers **positive**: Synaptophysin, chromogranin-A, chromogranin-B, CD56, NSE
 - Specific tumors (prolactin) are negative with chromogranin-A but positive with chromogranin-B
- Hormone peptides: Prolactin (60%) most common (Golgi accentuation in some)
 - Less common: FSH, LH, ACTH, β -TSH, GH, Pit-1, β -subunit and α -subunit of glycoprotein hormones, SF1, calcitonin
- May be mono- (33%), pluri- (48%), or nonhormonal (19%) adenoma

Electron Microscopy

- Intracytoplasmic neurosecretory granules
 - Number, size, shape, and type of granules dependent on tumor hormone production

DIFFERENTIAL DIAGNOSIS

Olfactory Neuroblastoma

- Ethmoid sinus, destructive tumor, lobular architecture, syncytial architecture, neurofilament background, rosette formation, prominent nucleoli and mitoses in high-grade tumors
- **Positive**: Chromogranin, synaptophysin, CD56, S100 protein (sustentacular); usually **negative** with keratin and peptide markers

Ewing Sarcoma/PNET

- Small round blue cell tumor, sheets, tumor necrosis; finely distributed chromatin, mitoses
- **Positive**: FLI-1, CD99, SNF5, NSE, β -catenin (membrane); **negative**: Chromogranin, keratin (usually)

Neuroendocrine Carcinoma

- High-grade malignant neoplasm, syncytial architecture, "salt and pepper" nuclear chromatin, mitoses, necrosis
- **Positive**: Keratin, chromogranin, synaptophysin, CD56

Meningioma

- Cellular tumors with whorled appearance, frequent calcifications, intranuclear cytoplasmic inclusions, coarse nuclear chromatin
- **Positive**: EMA, CK7; **negative**: Neuroendocrine and peptide markers

Mucosal Melanoma

- Dyscohesive epithelioid to spindled tumor cells, pigmented, intranuclear cytoplasmic inclusions, eccentric nuclei
- **Positive**: Melanoma markers (S100 protein, HMB-45, Melan-A, MITF); **negative**: Keratin, neuroendocrine markers

Squamous Cell Carcinoma

- Epithelial proliferation of squamous cells, intercellular bridges, dyskeratosis, significant pleomorphism, mitoses
- **Positive**: Keratin; **negative**: Neuroendocrine and peptide markers

Lymphoma

- Depends on B- or T-cell type: Cleaved, irregular nuclei, diffuse, sheets, high nuclear to cytoplasmic ratio, coarse nuclear chromatin, prominent nucleoli, mitoses, necrosis
- **Positive**: Lymphoid markers; **negative**: Keratin, neuroendocrine markers

DIAGNOSTIC CHECKLIST

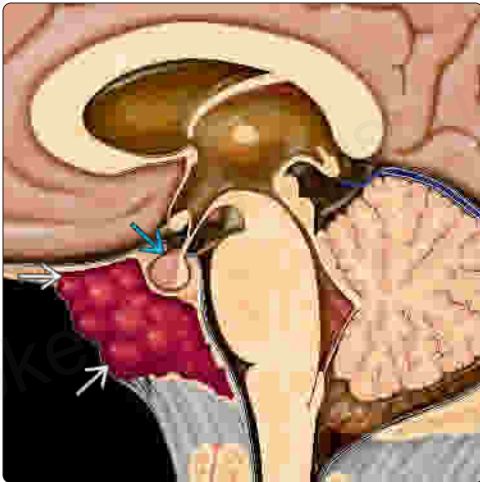
Pathologic Interpretation Pearls

- **Always** think of ectopic pituitary adenoma in sphenoid sinus tumor

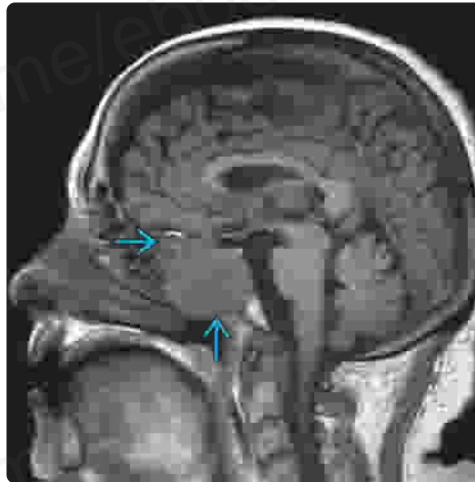
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Anatomic Graphic Showing Sphenoid Tumor

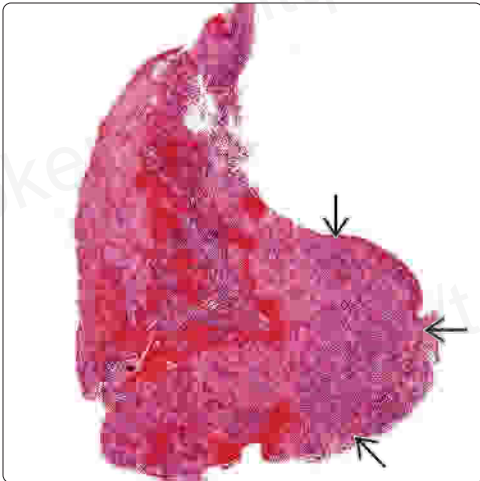


MR of Sphenoid Pituitary Adenoma

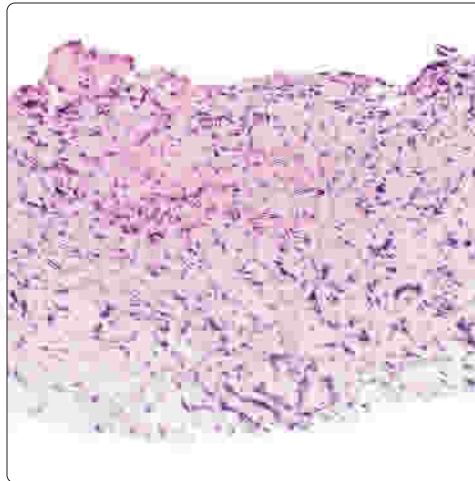



(Left) This is a diagrammatic representation of an ectopic pituitary adenoma. The sphenoid sinus is filled with tumor , expanding into the nasopharynx, but there is a completely normal pituitary , without any bony destruction. (Right) Sagittal T1-weighted FLAIR MR shows a large mass filling the sella and the sphenoid sinus . While helping confirm the diagnosis of a pituitary adenoma, the radiographic appearance is not diagnostic.

Polypoid Tumor Mass

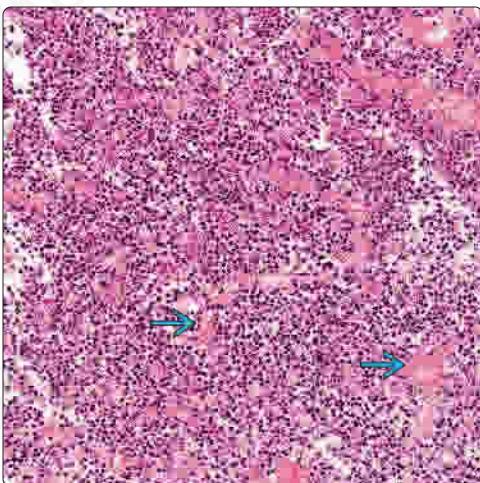


Heavy Stromal Fibrosis With Neoplastic Cells

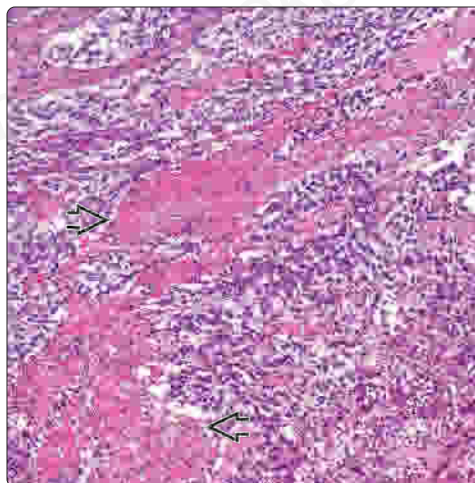




(Left) By macroscopic examination, the tumors tend to be polypoid or pedunculated masses. Most are solitary lesions. This tumor is < 1 cm. The surface epithelium is denuded, with a small round blue cell infiltrate . (Right) There is often remarkable fibrosis, nearly completely obscuring the true neoplasm, which shows a population of small cells in an infiltrative pattern. Immunohistochemistry is usually required in this setting.

Vaguely Trabecular Architecture



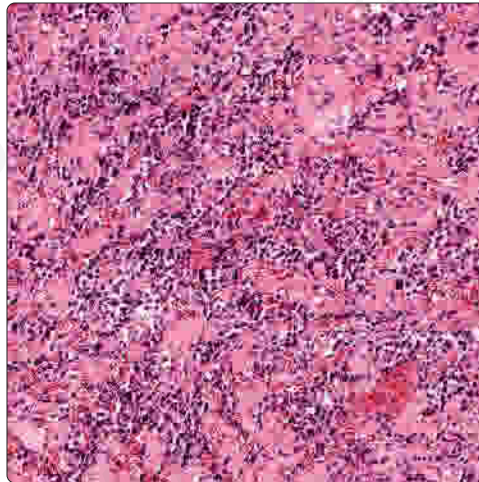
Tumor Necrosis



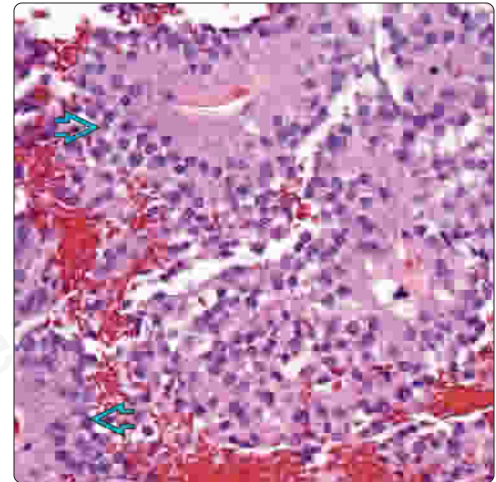
(Left) A solid cellular tumor is seen in this field, although delicate fibrovascular septa  can be seen throughout. In many cases, a dilapidated or degenerated appearance can be seen. (Right) Tumor necrosis  can be seen in a pituitary adenoma, and does not equate to a malignant lesion. This is an important consideration when evaluating the tumors within the differential diagnosis.

(Left) As seen here, an organoid neoplasm is separated by quite remarkable extracellular stromal hyalinization with blood. At this power, many small round blue cell tumors should be considered in the differential diagnosis. **(Right)** Multiple patterns can be seen within a pituitary adenoma. In this focus, pseudorosettes are noted.

Organoid Neoplastic Proliferation

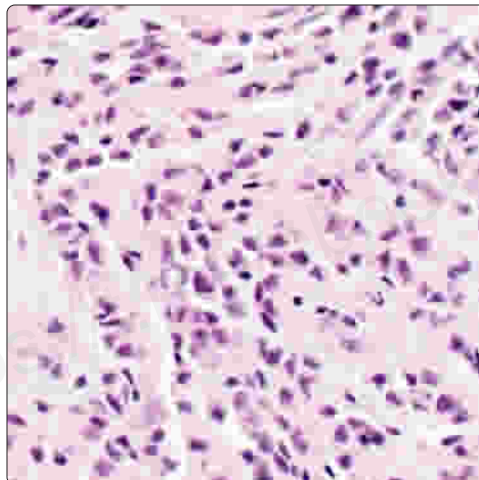


Pseudorosettes

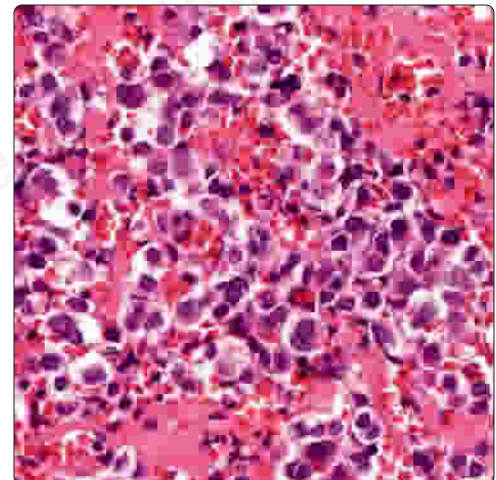


(Left) A solid to single cell infiltrative pattern is seen in this pituitary adenoma. The neoplastic cells have a plasmacytoid to rhabdoid appearance. **(Right)** These polygonal cells are arranged in a loose alveolar to festoon arrangement. The cells show focal binucleation, delicate, finely clumped chromatin, and isolated nucleoli. The cytoplasm is eosinophilic. There is a background of blood.

Plasmacytoid Tumor Appearance

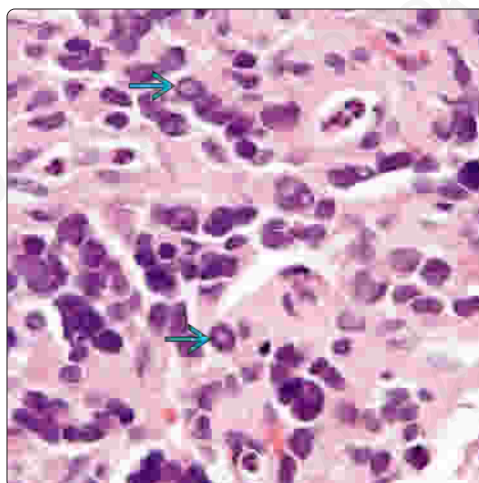


Mildly Polygonal Pleomorphic Cells

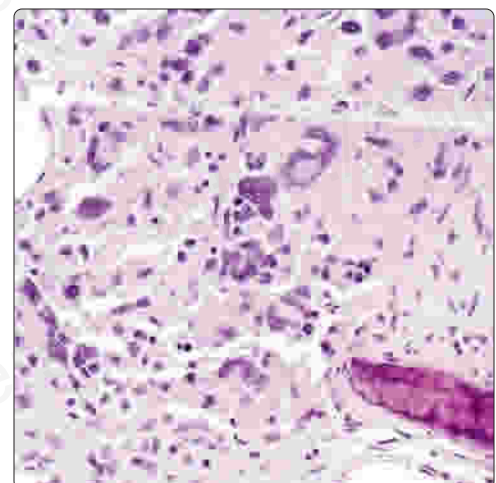


(Left) Intranuclear cytoplasmic inclusions can be seen, showing a well-formed membrane-lined inclusion. Meningioma and melanoma frequently also show inclusions. **(Right)** Profound nuclear pleomorphism can be seen in any endocrine organ neoplasm, as seen in this ectopic pituitary adenoma. Note the spicule of bone, since bony destruction can be present.

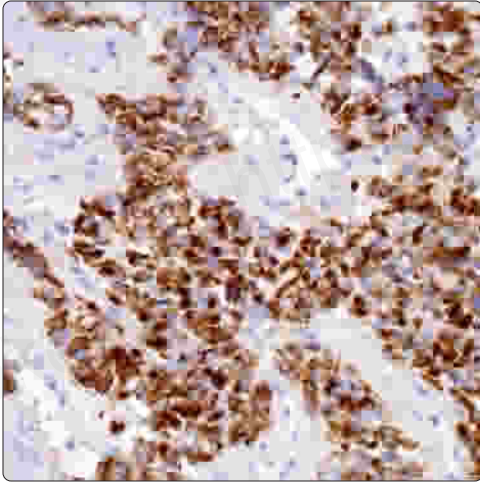
Intranuclear Cytoplasmic Inclusions



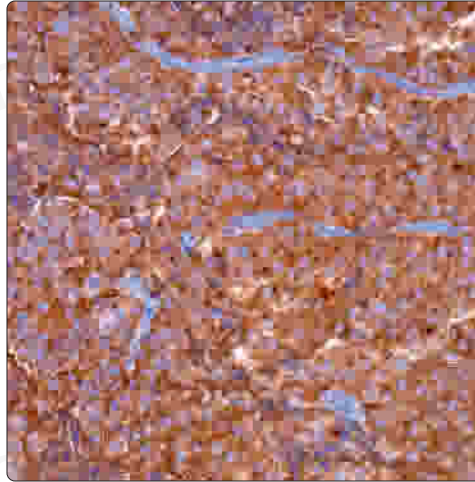
Profound Pleomorphism



CK-PAN Golgi Reaction

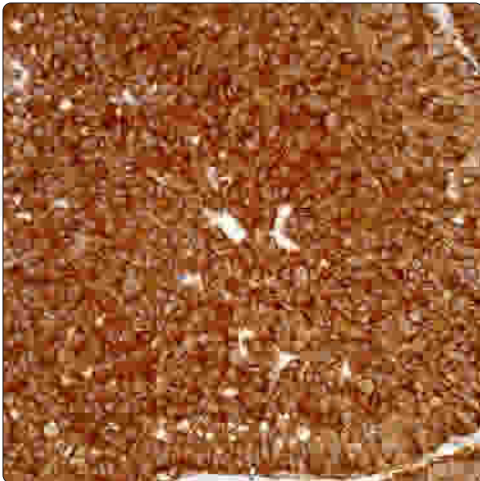


Cytoplasmic and Dot-Like Synaptophysin Reaction

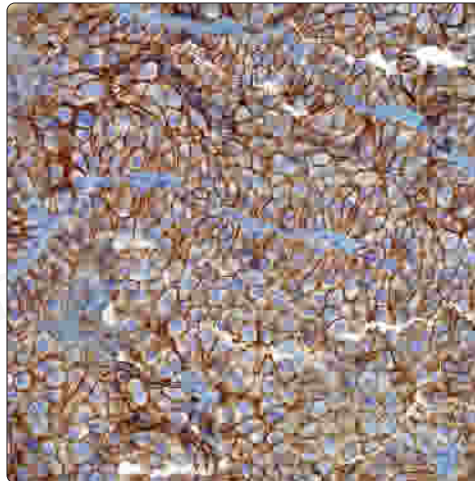


(Left) It is not uncommon to have a dot-like perinuclear (Golgi) pattern of immunoreactivity in this neuroendocrine-type neoplasm. This image shows a pancytokeratin reaction. (Right) A variety of different patterns of immunoreactivity can be seen with various neuroendocrine-type markers. The synaptophysin in this tumor shows both a cytoplasmic and Golgi (dot-like) positivity.

Chromogranin Immunoreactivity

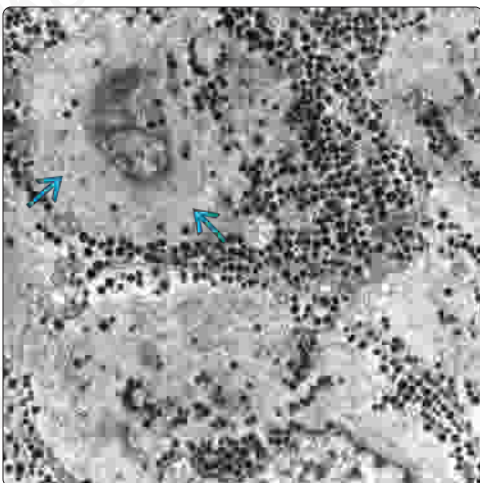


Membranous CD56 Immunoreactivity

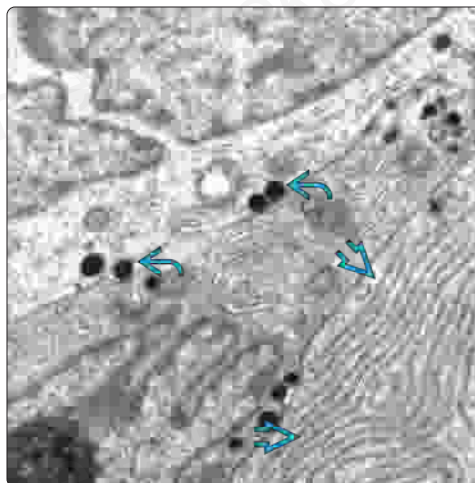


(Left) The chromogranin reaction may be cytoplasmic, granular, linear to membranous, or dot-like in a pituitary adenoma. This case shows a granular cytoplasmic reaction. (Right) Strong, diffuse, membranous reactivity in the neoplastic cells with CD56 in this pituitary adenoma. Cytoplasmic reaction can also be seen with CD56.

ACTH-Producing Adenoma



Adenoma of Prolactin-Producing Tumor



(Left) In this functioning corticotroph cell adenoma adrenocorticotrophic hormone (ACTH) (densely granulated), the cytoplasm is densely populated with pleomorphic secretory granules ranging from 250-500 nm. Perinuclear bundles of intermediate filaments (Crooke change) are diagnostic. (Right) A prolactin-secreting tumor cell is seen with large round cytoplasmic electron dense granules (200-300 nm in diameter), prominent rough endoplasmic reticulum, and misplaced lateral cell wall granule exocytosis.

KEY FACTS

TERMINOLOGY

- Benign neoplasm of meningotheial cells
 - Arachnoid cells from arachnoid granulations or pacchionian bodies lining sheaths of nerves and vessels through skull foramina

CLINICAL ISSUES

- ~ 0.2% of sinonasal tract and nasopharynx tumors
- Female > male (1.2:1)
 - Women older by over a decade
- Mean age: 40-48 years
- Mixed nasal cavity and paranasal sinuses (majority)
- Good outcome: 10-year survival (80%)

IMAGING

- Must exclude direct CNS extension

MICROSCOPIC

- Infiltrative growth of neoplastic cells, including soft tissue and bone
- Meningothelial (syncytial) lobules of neoplastic cells without distinct borders
- Whorled architecture common
- Psammoma bodies





ANCILLARY TESTS

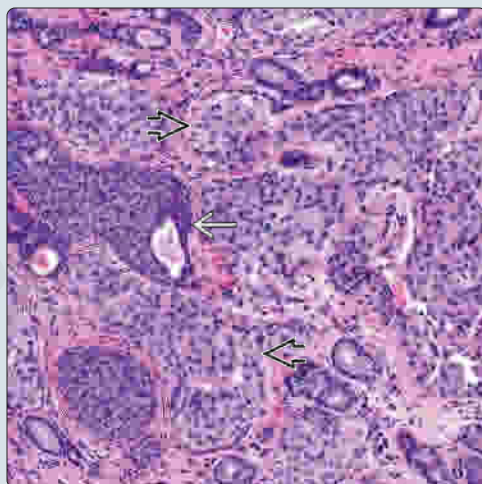
- **Positive:** EMA, cytokeratin and CK7 (patchy, ring-shaped staining surrounding prepsammomatous areas), CAM5.2

TOP DIFFERENTIAL DIAGNOSES

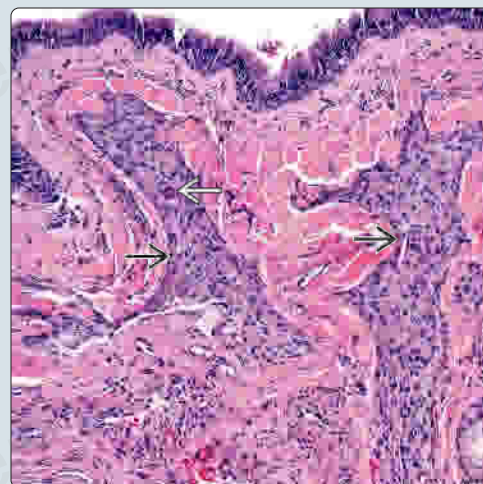
- Angiofibroma
- Aggressive psammomatoid ossifying fibroma
- Olfactory neuroblastoma
- Melanoma
- Paraganglioma

Blending of Meningioma and Squamous Epithelium


(Left) There is a very intimate blending between the meningioma  and the surface squamous epithelium  lining this part of the nasal cavity. The morphologic similarity is quite close. (Right) There is an intact respiratory epithelium overlying a meningothelial proliferation  set within a heavily collagenized stroma. A psammoma body  is noted within the proliferation.

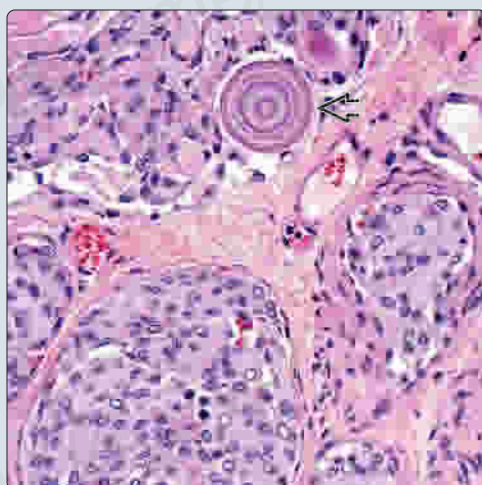


Intact Respiratory Epithelium Overlying Meningioma

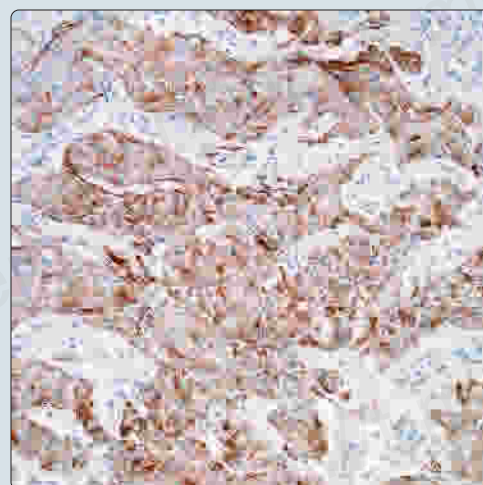


Meningothelial Meningioma

(Left) There is a meningothelial whorled and sheet-like distribution to this meningioma. Numerous intranuclear cytoplasmic inclusions are noted, while a well-formed psammoma body  is intimately associated with the tumor. (Right) The neoplastic cells will show a variable reaction with EMA, here shown as a strong cytoplasmic reaction. Note that not all tumor cells stain with the same intensity.



EMA(+) Reaction



TERMINOLOGY

Definitions

- Benign neoplasm of meningotheial cells within nasal cavity, sinonasal tract, and nasopharynx

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Arachnoid cells from arachnoid granulations or pacchionian bodies lining sheaths of nerves and vessels through skull foramina

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~ 0.2% of sinonasal tract and nasopharynx tumors
 - 20% of meningiomas have extracranial extension
- Age
 - Mean: 40-48 years
 - Women generally older than men by over a decade
- Sex
 - Female > male (1.2:1)

Site

- Mixed nasal cavity and paranasal sinuses (majority)
- Nasal cavity alone (~ 25%)
- Frontal sinus most commonly affected in isolation
- Majority are left sided

Presentation

- Mass, obstruction, discharge, and epistaxis
- Sinusitis, pain, headache, seizure activity
- Exophthalmos, periorbital edema, visual changes, ptosis

Treatment

- Surgical approaches
 - Complete surgical removal (although difficult at times)

Prognosis

- Good outcome: 10-year survival (80%)
- Recurrences develop (usually < 5 years after primary)

IMAGING

Radiographic Findings

- Must exclude direct CNS extension from en plaque tumor
- Bony sclerosis with focal destruction of bony tissues
- Widening of suture lines and foramina at base of skull

MACROSCOPIC

General Features

- Intact surface mucosa but infiltrative into bone
- Multiple fragments of grayish, white-tan, gritty, firm to rubbery masses
- Many are polypoid

Size

- Range: 1-8 cm; mean: 3.5 cm

MICROSCOPIC

Histologic Features

- Infiltrative growth of neoplastic cells, including soft tissue and bone
- Meningothelial (syncytial) lobules of neoplastic cells without distinct borders
- Whorled architecture
- Psammoma bodies or pre-psammoma bodies
- Epithelioid cells with round to regular nuclei and even nuclear chromatin
- Intranuclear cytoplasmic inclusions (invaginations)
- Histologic subtypes can be seen
 - Transitional, metaplastic, psammomatous, atypical

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** EMA, cytokeratin and CK7 (patchy, ring-shaped staining surrounding prepsammomatous areas), CAM5.2
- **Weak positive:** S100 protein, CEA-M, Bcl-2, progesterone receptor
- **Negative:** GFAP, chromogranin, synaptophysin

DIFFERENTIAL DIAGNOSIS

Angiofibroma

- Males only; nasopharynx; collagenized stroma, stellate stromal cells, haphazard vessels (staghorn)

Aggressive Psammomatoid Ossifying Fibroma

- Young patients; abundant psammoma bodies; osteoclasts and osteoblasts; compact to storiform stroma

Olfactory Neuroblastoma

- Cribriform plate; lobular growth; small cells with scant cytoplasm; fibrillar background; rosette/pseudorosette formations

Melanoma

- Protean mimic; intranuclear cytoplasmic inclusions; prominent nucleoli; melanoma markers positive

Paraganglioma

- Rare in sinonasal tract; nested architecture, basophilic cytoplasm; S100 protein sustentacular and chromogranin paraganglia reaction

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Ameloblastoma

KEY FACTS

TERMINOLOGY

- Locally aggressive benign epithelial odontogenic neoplasm

CLINICAL ISSUES

- Older age (6th-8th decades) at presentation than gnathic counterparts
- Male > Female (4:1)
- Symptoms are nonspecific, including unilateral enlarging mass, sinusitis, nasal obstruction, epistaxis
- Sinonasal cavity or maxillary sinus, with potential extension into adjacent areas
- Excellent, but requires long-term clinical follow-up to manage recurrences (up to 25%)

MICROSCOPIC



- Polypoid mass is most common
- Basal cells arranged in anastomosing strands (plexiform pattern)

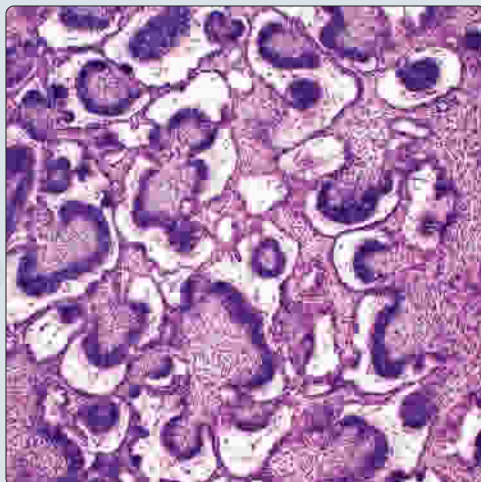
- Reverse polarity of basal columnar cells (a.k.a. Vickers-Gorlin change) with subnuclear vacuolization
- Central, loosely arranged stellate reticulum, which can become cystic
 - Cells can be spindle shaped, basaloid, granular, or show squamous (acanthomatous) differentiation
- Many histologic types: Plexiform, ameloblastic, and acanthomatous are most common in sinonasal tract
- Pleomorphism and mitoses are rare

TOP DIFFERENTIAL DIAGNOSES

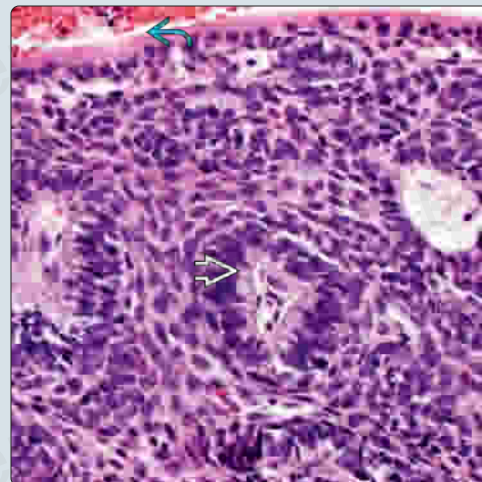
- Basaloid squamous cell carcinoma
- Basal cell adenoma
- Pleomorphic adenoma
- Adenoid cystic carcinoma
- Sinonasal nonintestinal/nonsalivary gland adenocarcinoma

Classical Ameloblastoma


(Left) Hematoxylin and eosin shows the classic palisading of the nuclei with typical reverse polarity and subnuclear clearing. The stellate reticulum has a syncytial architecture. Edema is focally noted, creating a separation artifact. (Right) Intact respiratory epithelium  overlies the stellate reticulum with abrupt areas of columnar cells with reverse polarity and prominent subnuclear vacuoles .

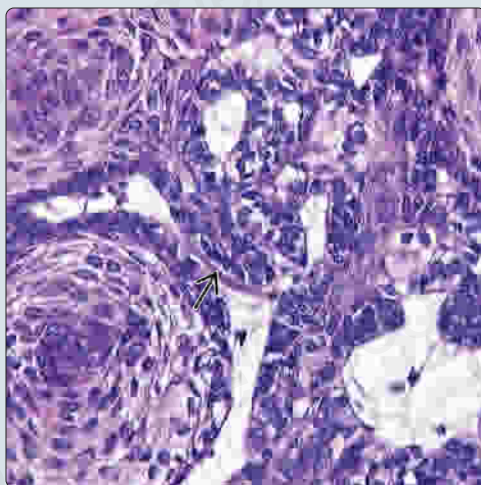


Subepithelial Proliferation

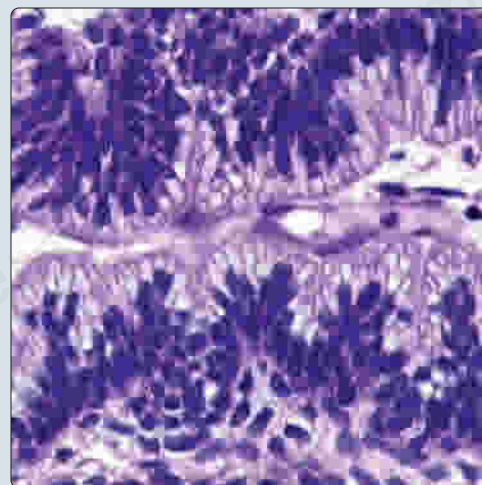


Acanthomatous Stellate Reticulum

(Left) The stellate reticulum in the center of the proliferation islands shows a well-developed squamous differentiation in this ameloblastoma. Columnar cells with peripheral palisading  are seen. (Right) Note the prominent reverse polarity of the nuclei. The columnar nuclei are set within tall cells, illustrating the subnuclear vacuolization. The vacuoles are lined up against fibrovascular cores. The subnuclear vacuoles are the classical Vickers-Gorlin change.



Vickers-Gorlin Subnuclear Vacuolization



TERMINOLOGY**Definitions**

- Locally aggressive, benign, epithelial odontogenic neoplasm arising from remnants of odontogenic epithelium

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Rare
- Age
 - Mean: 6th to 8th decades
 - Older than gnathic counterparts
- Sex
 - Male > female (4:1)

Site

- Sinonasal cavity or maxillary sinus, with possible extension into other location
 - May present with combined involvement

Presentation

- Symptoms are nonspecific, including unilateral enlarging mass, sinusitis, nasal obstruction, epistaxis

Treatment

- Surgical approaches
 - Conservative surgery or curettage to more aggressive surgery (radical maxillectomy), patient status dependent
 - Surgical excision with adequate margin is treatment of choice
- Radiation
 - Not used as first-line treatment

Prognosis

- Excellent, but long-term clinical follow-up is essential to manage potential recurrences
- Recurrence, usually within 1 year of initial surgery, occurs in up to 25%
- May die **with** but not **from** disease

IMAGING**General Features**

- Multilocular, expansile lucency of bone (may appear destructive)
- Unilateral maxillary sinus opacification

MACROSCOPIC**General Features**

- Polypoid mass is most common
- Glistening, gray-white, pink, or yellow-tan
- Rubbery to granular
- Bone can be present

Size

- Range: Up to 9 cm

MICROSCOPIC**Histologic Features**

- Blend of ameloblasts and epithelial cells (enamel organ)
- Intact overlying respiratory epithelium
- Ameloblastic cells are palisaded about periphery of tumor nests in jigsaw-like configuration
- Basal cells arranged in anastomosing strands (plexiform pattern)
- Reverse polarity of basal columnar cells (a.k.a. Vickers-Gorlin change) with subnuclear vacuolization
 - Nuclei displaced away from basement membrane and are hyperchromatic
- Central, loosely arranged stellate reticulum, which can become cystic
 - Cells can be spindle shaped, basaloid, granular, or show squamous (acanthomatous) differentiation
- Mitotic activity and cellular pleomorphism are rare
- Many histologic types: Plexiform, ameloblastic, and acanthomatous are most common in sinonasal tract
 - Desmoplastic and granular cell types are less frequent

DIFFERENTIAL DIAGNOSIS**Basaloid Squamous Cell Carcinoma**

- Basaloid peripheral palisade with abrupt squamous differentiation; may mimic acanthomatous pattern

Basal Cell Adenoma

- Small, basaloid cells with peripheral palisade; no subnuclear vacuolization; lacks stellate reticulum

Pleomorphic Adenoma

- Tubuloglandular structures; myoepithelial plasmacytoid cells; myxochondroid matrix

Adenoid Cystic Carcinoma

- Cribriform pattern; mucoid pseudoglandular structures; reduplicated basement membrane

Sinonasal Nonintestinal-Type Adenocarcinoma

- Glandular malignancy, with variable degrees of pleomorphism
- Lacks subnuclear vacuoles and stellate reticulum

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Lobular Capillary Hemangioma (Pyogenic Granuloma)

KEY FACTS

TERMINOLOGY

- Benign overgrowth of capillary loops with obviously vascular phenotype

ETIOLOGY/PATHOGENESIS

- Trauma: Nose picking, nasal packing, cauterization, shaving/hair removal, nonspecific microtrauma
- Hormones: Increased in pregnancy, oral contraceptive use

CLINICAL ISSUES

- Mucosal hemangiomas represent ~ 10% of all head and neck hemangiomas
- Peak: Adolescent males and reproductive females
 - Pediatric age: M > > F
 - Reproductive years: F > > M
- Oral cavity (60%), nasal cavity (30%)
 - Anterior nasal septum (Little or Kiesselbach area; 60%)
- Rapidly growing, painless, hemorrhagic mass
- Epistaxis is most common symptom for nasal lesions (95%)

- Biopsy should be **avoided** due to profound epistaxis
- Endoscopic resection is treatment of choice, removing rim of normal tissue

MICROSCOPIC

- Polypoid, nodular, diffuse, or sessile mass
- Ulcerated surface with fibrinous exudate
- Collarette of epithelium around areas of ulceration
- Circumscribed, lobular arrangement of capillaries around central vessel
- Stroma is fibromyxoid to edematous, then hyalinized



ANCILLARY TESTS

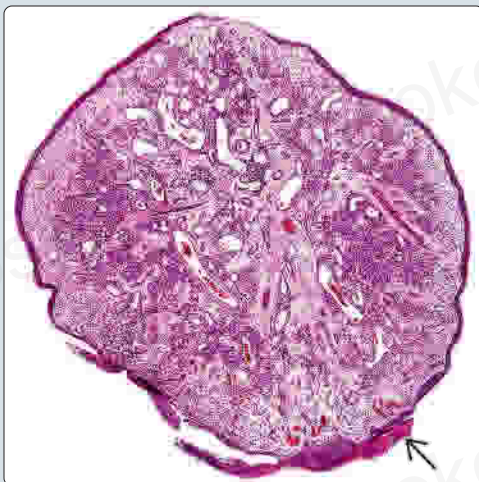
- Endothelial cells: CD31, CD34, FVIIIIRAg, vimentin

TOP DIFFERENTIAL DIAGNOSES

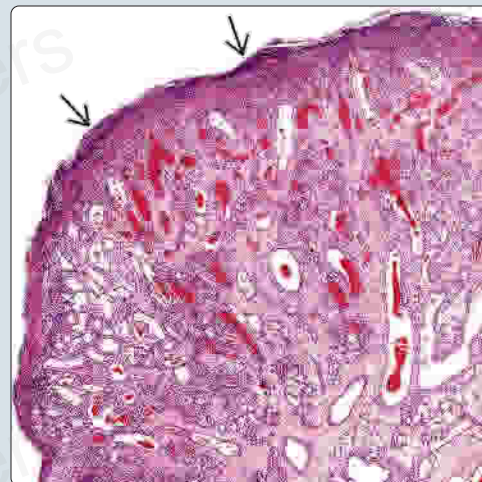
- Sinonasal polyps, nasopharyngeal angiofibroma, glomangiopericytoma, angiosarcoma, granulation tissue, Kaposi sarcoma, glomus tumor

Polypoid Mass



(Left) Lobular capillary hemangioma (LCH) tends to be very polypoid (pedunculated), nodular masses. The surfaces are frequently ulcerated . A vague lobularity can be easily identified, even at this magnification. (Right) The surface is ulcerated  in this LCH. The rich vascularity of the proliferation is noted in the stroma.

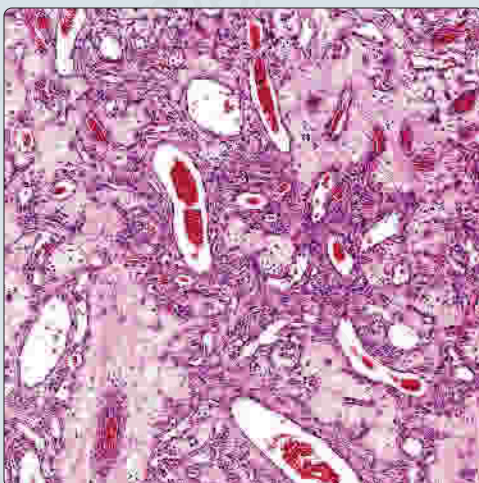


Surface Ulceration

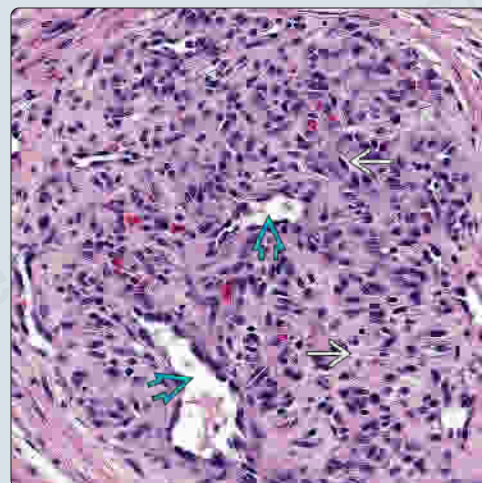


Lobular Arrangement of Vessels

(Left) There is a lobular arrangement of capillaries lined by endothelial cells. A central vessel shows branching lumina. There is intimate association with spindle pericytes. Note small arteries and veins in the stroma. (Right) This high-power image highlights the well-circumscribed, lobular arrangement of capillaries. The lobule has clusters of endothelial-lined capillaries with lumina that are prominent  to slit-like . The cells are bland.



Lobular Architecture of Capillaries



TERMINOLOGY

Abbreviations

- Lobular capillary hemangioma (LCH)

Synonyms

- Pyogenic granuloma (PG)
 - While taxonomically inaccurate, PG is entrenched in medical literature
 - It is **not** purulent, infectious, or granulomatous
- Epulis gravidarum

Definitions

- Benign overgrowth of capillary loops with obviously vascular phenotype

ETIOLOGY/PATHOGENESIS

Etiology

- Trauma or injury
 - Nose picking, nasal packing, cauterization, shaving/hair removal, nonspecific microtrauma
 - Nasal packing is commonly used for nasal bleeding and postoperative hemostasis
- Hormones
 - Increased in pregnancy or oral contraceptive use
 - Profound metabolic and endocrine changes in pregnancy seem to contribute to rapid growth

Familial Association

- Hemangioma(s) in sinonasal tract and multiple cutaneous hemangiomas
 - Consider Sturge-Weber or von Hippel-Lindau

CLINICAL ISSUES

Epidemiology

- Incidence
 - Mucosal hemangiomas account for ~ 10% of all head and neck hemangiomas
 - ~ 30% develop in nasal cavity
 - Account for ~ 25% of all nonepithelial tumors of sinonasal tract
- Age
 - Wide range: 1-65 years; mean: 30 years
 - Peak: Adolescent males and reproductive females
- Sex
 - Female > male (2:1)
 - Pediatric age (up to 18 years): Male >> female
 - Reproductive years: Female >> male
 - > 40 years: Equal gender distribution

Site

- Order of frequency in head and neck
 - Oral cavity (60%), nasal cavity (30%), paranasal sinuses (8%), and nasopharynx (2%)
 - Oral: Gingiva (75%), lips, tongue, buccal mucosa
 - Nasal cavity: Anterior nasal septum (Little area; 60%), nasal vestibule, turbinate (tip)

Presentation

- Epistaxis (nasal) is most common symptom (95%)
 - Spontaneous, intermittent, and unilateral bleeding

- Bleed easily with minor trauma
- Nasal obstruction (35%) in larger tumors
- Rapidly growing, painless, hemorrhagic mass
- Symptoms usually present for short duration, as tumor develops rapidly
- Sinus lesions present with sinusitis, proptosis, mass, anesthesia, pain

Endoscopic Findings

- Rhinoscopy shows well-defined, sessile or pedunculated, dark red-brown to purplish mass
- Ulcerated, friable surface with fibrinous exudate

Natural History

- May spontaneously involute after pregnancy

Treatment

- Options, risks, complications
 - Biopsy should be **avoided**, if possible, due to profound epistaxis
 - Preoperative radiology studies part of planning
 - Confirm nature and extent of lesion, avoiding biopsy and open procedures
 - Aplasia of nasal cartilages may cause disfigurement in young patients
 - Pregnancy-related tumors will spontaneously involute after delivery
- Endoscopic resection is treatment of choice
 - Rim of normal mucosa/submucosa
 - Removal to epichondrium prevents recurrence
- Preoperative embolization for large lesions

Prognosis

- Excellent long-term clinical outcome
 - Fatal exsanguination is reported
- Multiple recurrences (~ 20%) more common in children

IMAGING

Radiographic Findings

- US: Confirms anatomic site, extent, and vascular nature of process
- CT: Intensely enhancing mass within nasal cavity (septum)
- MR: Tumor with high signal intensity on T2-weighted images or after gadolinium contrast
- Angiography identifies feeder vessel(s), useful in presurgical embolization

MACROSCOPIC

General Features

- Polypoid (pedunculated), nodular, diffuse, or sessile mass (latter in children)
- Soft and compressible submucosal mass
- Ulcerated surface (40% of cases), partially covered by yellow to white fibrinous exudate
- Pink-red, blue-purple, gray-tan (depends on congestion)

Size

- Range: 1-8 cm; mean: 1.5 cm

Lobular Capillary Hemangioma (Pyogenic Granuloma)

MICROSCOPIC

Histologic Features

- Polypoid, with high cellularity
- Surface ulceration with exudate and fibrin
 - Collarette of epithelium is seen on either side of ulcerated areas
 - Secondary, nonspecific changes can be present
 - Stromal edema, capillary dilation, inflammation, granulation tissue reaction
- Circumscribed, lobular arrangement of capillaries
 - Lobule has cluster of endothelial-lined capillaries
 - Lumina can be absent, slit-like to prominent
 - Endothelial cells range from plump to flattened
 - Immature to mature vessels
 - Bland nuclei surrounded by eosinophilic cytoplasm
 - Small capillaries and venules arranged around central vessel
 - May show branching lumina
 - Intimate association of spindled pericytes within perivascular spaces
 - Small arteries and veins may be present adjacent to lobules
- Surrounding stroma is fibromyxoid to edematous, but may be hyalinized, especially with chronicity
- Mixed inflammatory cells and extravasated erythrocytes are usually present
 - Small lymphocytes, plasma cells, mast cells, neutrophils
 - Arranged on gradient: Greater at surface, less at center
- Mitotic figures easily identified, often increased
 - Atypical mitoses are absent

Subtypes

- **Cavernous hemangioma**
 - Very uncommon in nasal cavity, but
 - Large, open, cystic, or cavernous spaces
 - Thin-walled spaces lined by bland endothelial cells with scant stroma
 - Erythrocytes in spaces
 - Variably intense chronic inflammatory infiltrate in stroma
- **Hemangiomatosis**
 - Extensive, frequently involving bone and adjacent skin and sinuses
 - Vascular channels of variable size and shape with flat endothelial cells, possibly containing fat

ANCILLARY TESTS

Histochemistry

- Reticulin: Outlines endothelial cells
- Elastic: Identifies fibers in vascular walls

Immunohistochemistry

- Endothelial cells: CD31, CD34, FVIIIIRAg, vimentin
- Perivascular cells: Smooth muscle and muscle-specific actins
- Pericytes: Collagen IV and laminin (around endothelial cells)
- Variably positive with estrogen and progesterone receptors

Genetic Testing

- Clonal deletion (21)(q21.2q22.12) is reported

DIFFERENTIAL DIAGNOSIS

Sinonasal Polyps

- Edematous/fibrotic stroma with limited mucoserous glands
- Haphazard vascular proliferation or become hemorrhagic
- Eosinophils predominate

Angiofibroma (Nasopharyngeal)

- Exclusively in males, arising from nasopharynx
- Variable vascular component from capillaries to muscle-walled vessels
- Hyalinized stroma with fine to coarse collagen deposition
- Spindle or stellate stromal cells with mast cells

Glomangiopericytoma

- Patternless to slightly fascicular arrangement of oval to spindled cells
- Richly vascularized tumor showing characteristic perivascular hyalinization
- Inflammatory infiltrate with mast cells and eosinophils

Angiosarcoma

- Widely infiltrative and destructive tumor
- Freely anastomosing vascular channels lined by atypical endothelial cells
- Increased mitotic figures and necrosis in high-grade tumors

Granulation Tissue

- More haphazard architecture, with significant inflammation
- Mitotic figures are common, but necrosis is not present

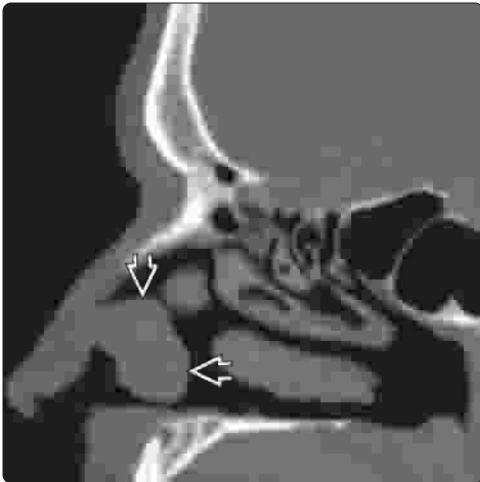
Vascular Lesions

- Kaposi sarcoma, intravascular papillary endothelial hyperplasia, vascular malformation, bacillary angiomatosis, glomus tumor, lymphangioma, telangiectasia
 - All are exceedingly rare in sinonasal tract, showing features similar to other anatomic sites
 - All lack lobular architecture

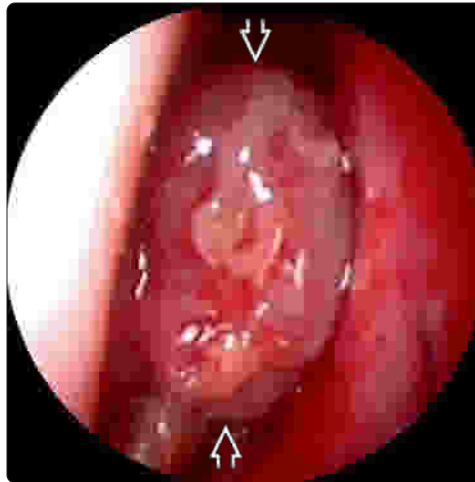
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CT: Little Area Mass

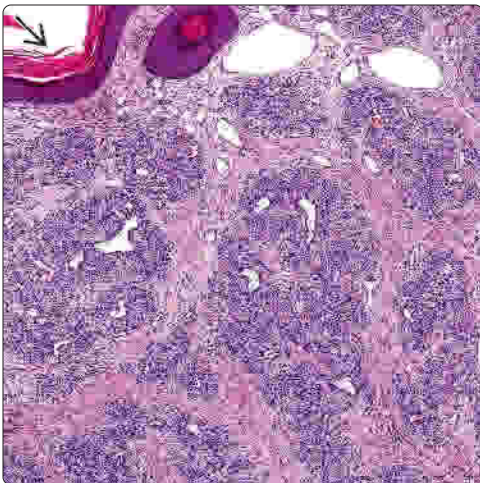


Rhinoscropy View of Polypoid Mass

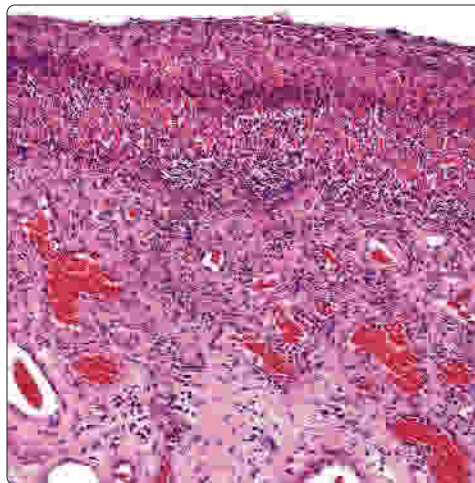


(Left) Kiesselbach triangle, or Little area, is the name for the confluence of 4 nasal arteries in the lower part of the anterior septum. This is the most common place for a LCH, shown here in a CT scan. (Right) Rhinoscopy shows a well-defined polypoid or pedunculated reddish mass within the nasal cavity. The surface shows erythema and ulceration, with a friable surface containing a fibrinous exudate. (Courtesy G.G. Calzada, MD.)

Intact Collarette of Epithelium

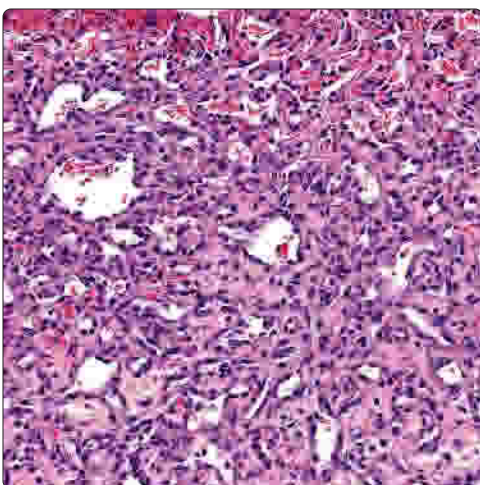


Ulceration With Fibrinoid Necrosis

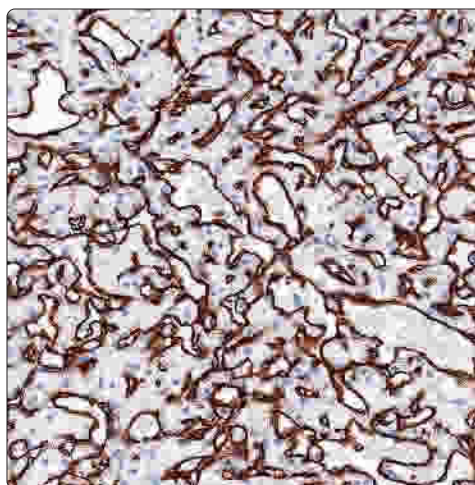


(Left) Part of the epithelial collarette is identified overlying the circumscribed, lobular arrangement of capillaries. Each lobule shows a cluster of endothelial-lined capillaries with variable lumina. A central vessel is noted. (Right) The surface is ulcerated and eroded with fibrinoid necrosis identified. Dilated vessels are noted immediately below. This portion could be part of granulation tissue or a LCH.

Haphazard Endothelial Proliferation



CD34 Highlights Endothelial Cells



(Left) There is a more haphazard arrangement to the endothelial cells lining the variably sized vessels. The vessels are mature to immature with bland endothelial cells. Intimate association of spindled pericytes is also noted. The stroma is slightly fibrous. (Right) The endothelial cells can be highlighted by CD34 (shown), along with CD31, FVIIIIRAg, and vimentin. The perivascular cells are highlighted by actins, with collagen IV and laminin surrounding them.

Schwannoma/Neurofibroma

KEY FACTS

TERMINOLOGY

- **Schwannoma:** Benign peripheral nerve sheath tumor showing differentiated Schwann cells
- **Neurofibroma (NF):** Schwann cell tumor with perineurial hybrid cells and intraneural fibroblasts

ETIOLOGY/PATHOGENESIS

- Association with neurofibromatosis type 1 (NF1): ~ 11%

CLINICAL ISSUES

- Mean: 5th-6th decades, younger in patients with NF1
- Ethmoid and maxillary sinuses (schwannoma)
- Nasal cavity and maxillary sinuses (NF)

MACROSCOPIC

- Well-delineated, polypoid, globular, firm to rubbery, yellow-tan mass, ~ 3 cm

MICROSCOPIC

- Submucosal mass with intact surface epithelium

- **Schwannoma:** Blending of cellular (Antoni A) with hypocellular (Antoni B) areas
 - Verocay bodies (palisaded nuclear aggregates)
 - Medium-sized ectatic vessels with marked hyalinization
- **NF:** Paucicellular circumscribed submucosal mass, often associated with nerve twigs; fusiform cells with fibrillar cytoplasm and spindle, wavy/buckled nuclei
 - Background of collagenized/myxoid stroma and mast cells

ANCILLARY TESTS

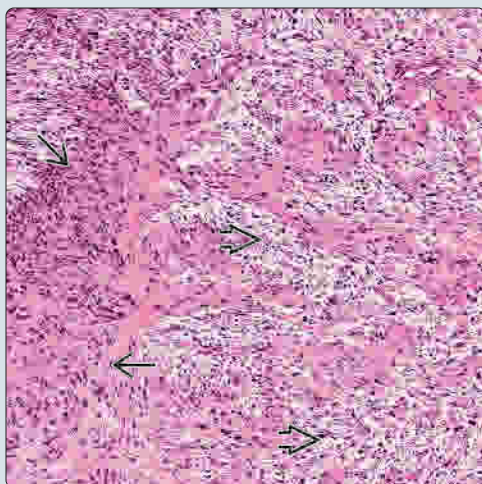
- Schwannoma: **Positive:** S100 protein, SOX10; focal GFAP and NSE; CD34 in perineurium
- NF: **Positive:** S100 protein, SOX10, NFP, GFAP, bcl-2; CD34 in perineurium

TOP DIFFERENTIAL DIAGNOSES

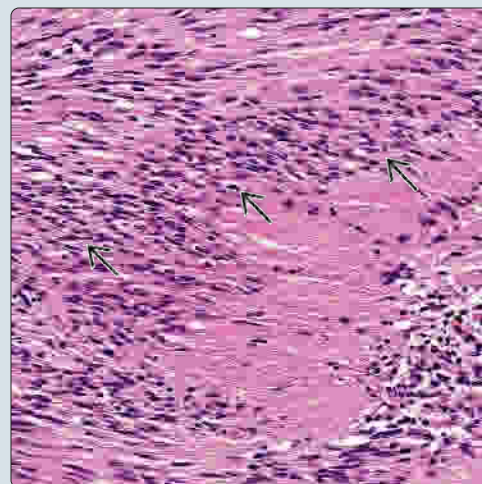
- Meningioma, leiomyoma, solitary fibrous tumor, fibrosarcoma, malignant peripheral nerve sheath tumor

Schwannoma With Hyper- and Hypocellular Areas

(Left) There is a juxtaposition and blending of cellular Antoni A areas [box] with hypocellular Antoni B areas [box]. The nuclei have palisading. Note the areas of myxoid-type change. (Right) This Antoni A area shows elongated nuclei stacked in neat rows [box] (palisade resembling a fortification) with Schwann cell cytoplasm in the center. This Verocay body is characteristic of schwannoma.

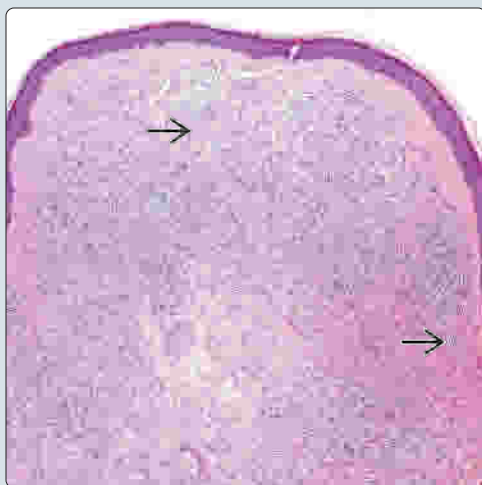


Schwannoma: Verocay Body

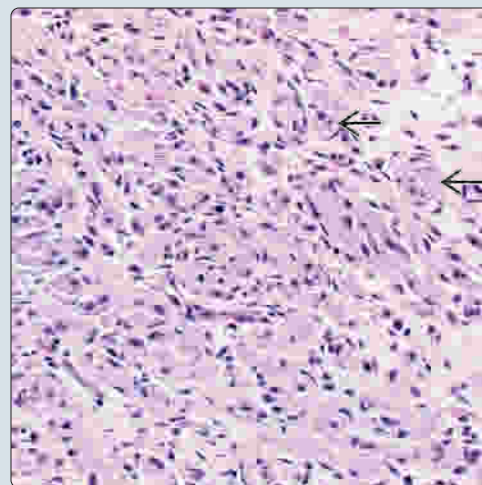


Neurofibroma: Subepithelial Proliferation

(Left) The surface epithelium is intact, overlying a spindled cell proliferation. Nerve twigs [box] and collagen fibers are noted as part of this neurofibroma. (Right) There are several small nerve twigs [box] embedded within this Schwann cell proliferation. The collagenized stroma also contains perineurites (perineurial cells) as part of a neurofibroma.



Neurofibroma: Blending of Schwann Cells and Fibroblasts



TERMINOLOGY**Synonyms**

- Benign peripheral nerve sheath tumor

Definitions

- **Schwannoma**: Benign peripheral nerve sheath tumor showing differentiated Schwann cells
- **Neurofibroma (NF)**: Schwann cell tumor with perineurial hybrid cells and intraneural fibroblasts

ETIOLOGY/PATHOGENESIS**Genetic Factors**

- Association with neurofibromatosis type 1 (NF1): ~ 11%

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Very rare in sinonasal tract
- Age
 - Mean: 5th-6th decades; younger in patients with NF1
- Sex
 - Equal gender distribution

Site

- Ethmoid and maxillary sinuses (schwannoma)
 - Involve branches of 5th (trigeminal) cranial nerve or autonomic nervous system
- Nasal cavity and maxillary sinuses (NF)
- Tend to develop along midline
- Rarely, expands into orbit, nasopharynx, pterygomaxillary fossa, cranial cavity

Presentation

- Nonspecific symptoms: Mass, obstruction, epistaxis, pain, headache, facial or orbital swelling

Treatment

- Complete excision is treatment of choice

Prognosis

- Benign tumor with very low recurrence potential
- Malignant transformation is exceptional (seen in NF1)

IMAGING**Radiographic Findings**

- Best study: T1WI MR with contrast and fat suppression
- Sharply and smoothly marginated soft tissue mass, lacking bone destruction

MACROSCOPIC**General Features**

- Unilateral, well-delineated, nonencapsulated polypoid mass
- Globular, firm to rubbery, yellow-tan mass
- Cut surfaces are myxoid and cystic, frequently with hemorrhage

Size

- Mean: 3 cm
- Range: Up to 7 cm

MICROSCOPIC**Schwannoma**

- Submucosal mass with intact surface epithelium
- Blending of cellular (Antoni A) with hypocellular (Antoni B) areas
 - Verocay bodies are palisaded nuclear aggregates
- Hypocellular areas with microcystic degeneration or reticular pattern
 - Degenerative changes may be quite prominent (histiocytes, cyst formation, hemorrhage)
- Fusiform cells with fibrillar cytoplasm and spindled, wavy/buckled nuclei
- Pleomorphism is limited and mitoses are rare
- Medium-sized ectatic vessels with marked hyalinization
- Glandular variant is rare in this location

Neurofibroma

- Paucicellular circumscribed submucosal mass, often associated with nerve twigs
- Spindled cells with curvilinear, dark-staining nuclei and scanty spindled cytoplasm
- Background of collagenized/myxoid stroma and mast cells

ANCILLARY TESTS**Immunohistochemistry**

- Schwannoma: **Positive**: S100 protein, SOX10; focal GFAP and NSE; CD34 in perineurium
- NF: **Positive**: S100 protein, SOX10, NFP, GFAP, bcl-2; CD34 in perineurium
- **Negative**: Keratin, desmin, SMA, CD117, nuclear β -catenin

DIFFERENTIAL DIAGNOSIS**Meningioma**

- Whorled architecture, intranuclear cytoplasmic inclusions; EMA(+) immunoreactivity

Leiomyoma

- Spindled cells, cigar-shaped nuclei, perinuclear clearing, short fascicles; actin immunoreactivity

Malignant Peripheral Nerve Sheath Tumor

- Greater degree of pleomorphism, necrosis, increased mitoses, destructive growth, S100 protein is often decreased or limited

Fibrosarcoma

- Cellular tumor, fascicular/herringbone architecture; **negative**: S100 protein and CD34



Solitary Fibrous Tumor

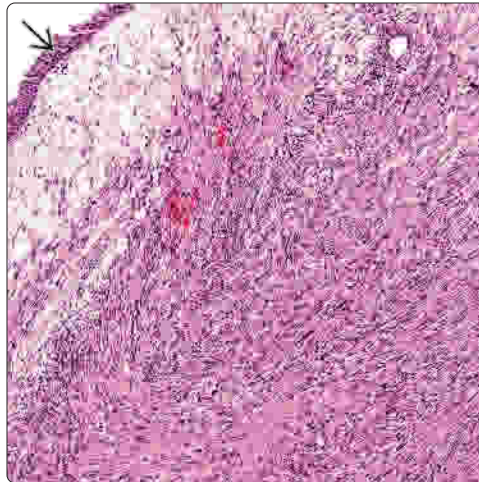
- Collagenized stroma with spindled cell tumor; strong CD34 and bcl-2, lacking S100 protein

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Fascicles of Schwannoma Below Surface

(Left) The surface epithelium is intact , with a submucosal proliferation of spindled neoplastic cells. They are arranged in long, sweeping fascicles, which expand into the subepithelial stroma. **(Right)** The cellularity of tumors can be quite variable. In this field, the tumor is overall hypocellular, although, areas of increased cellularity are still present. Histiocytes are seen . This is a typical schwannoma.

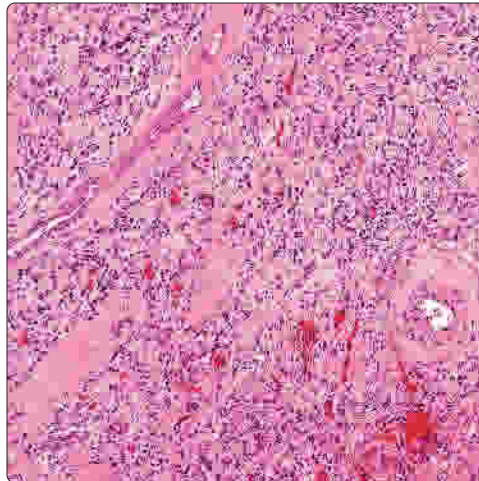


Blending of Cellular and Hypocellular Areas

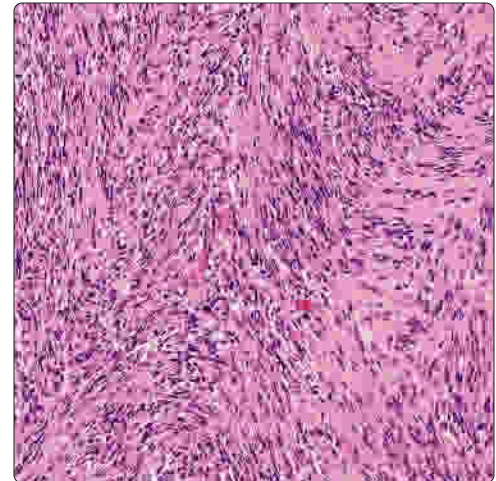


Perivascular Hyalinization



(Left) This is a hypocellular Antoni B area in which there are well-developed, medium-sized ectatic vessels with marked hyalinization of the wall. **(Right)** This is a cellular Antoni A area showing palisading and lined up nuclei. The cytoplasm is eosinophilic and fibrillar, surrounding spindled, buckled nuclei. There is no cytologic atypia.

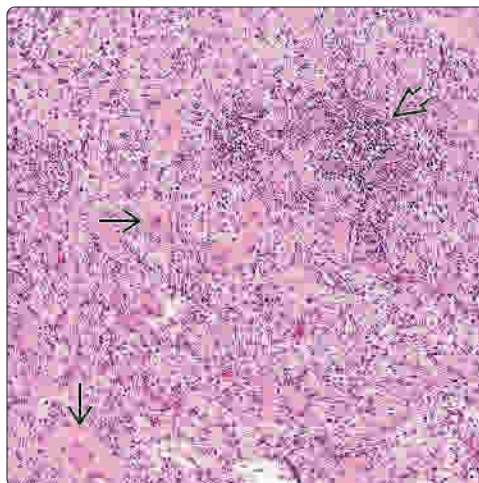


Palisading Nuclei in Schwannoma

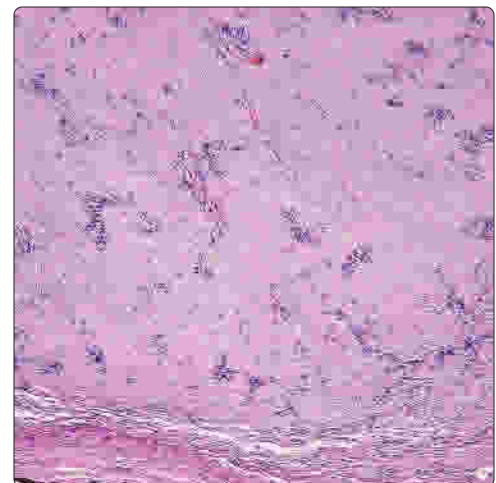


Inflammation and Perivascular Hyalinization

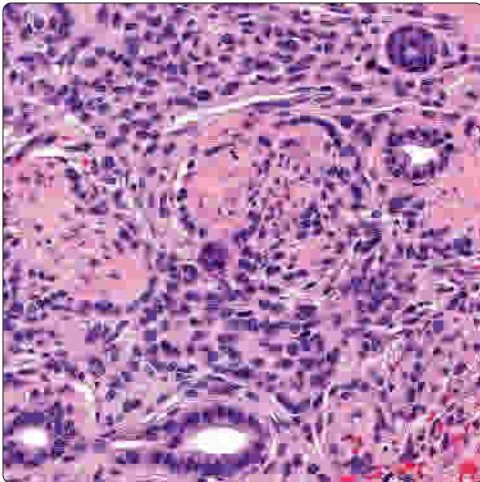
(Left) This hypocellular area of a schwannoma shows perivascular hyalinization  and focal chronic inflammation . **(Right)** There is a well-circumscribed border to this schwannoma. This entire field is quite hypocellular, showing only a few isolated areas with nuclear palisading.



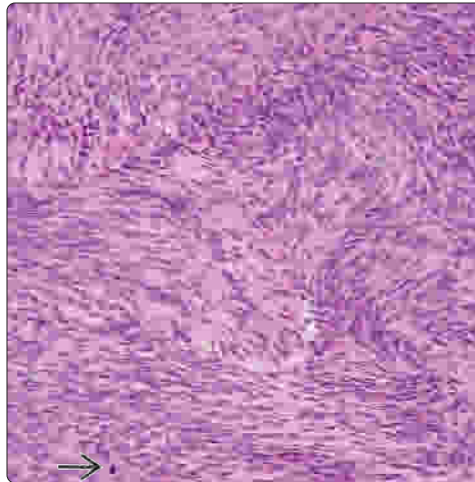
Hypocellular (Antoni B) Area in Schwannoma




Glandular Schwannoma

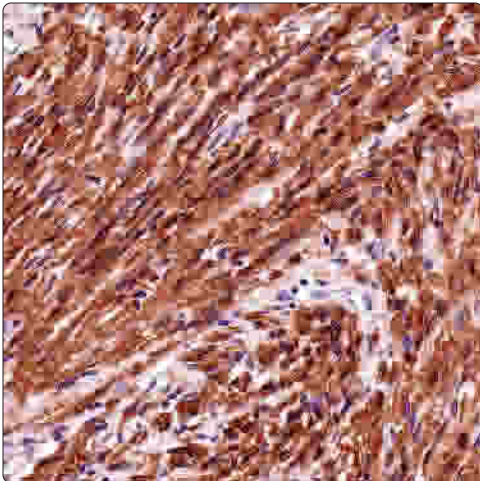


Cellular (Antoni A) Region in Schwannoma

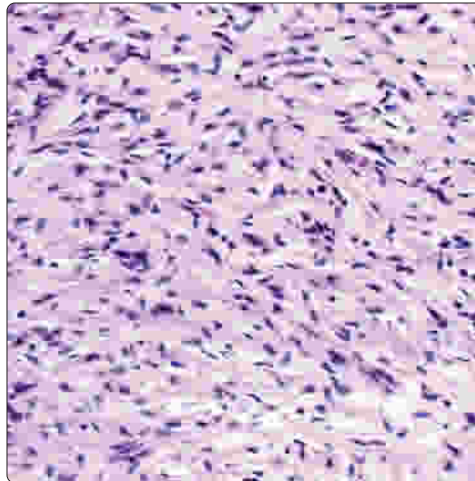


(Left) A glandular variant is very rare, composed of glandular profiles set intimately within the spindle cell, fusiform Antoni A area. Separation of native serous gland entrapment from glands that are part of the tumor is challenging. (Right) This part of the schwannoma was more cellular than other areas, showing an interlacing fascicular architecture. A mitotic figure  is noted but is not atypical.

Strong S100 Protein Reaction in Schwannoma

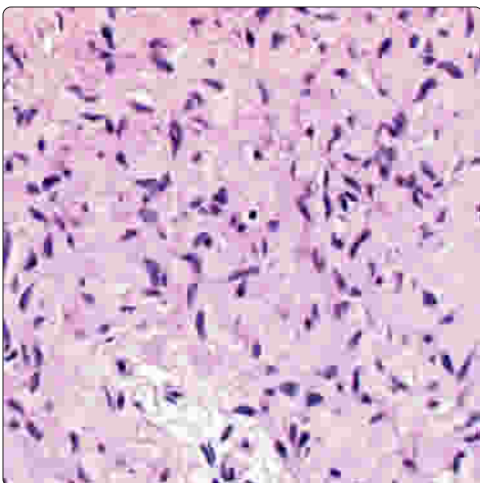


Neurofibroma and Schwannoma Hybrid

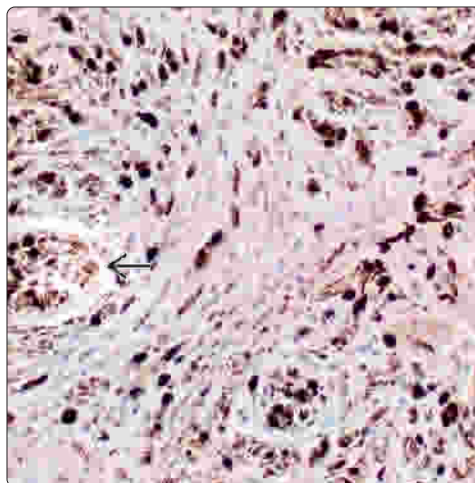



(Left) The neoplastic cells of a schwannoma are strongly and diffusely positive in both the nucleus and cytoplasm with S100 protein. A similar strong reaction can be seen in the cytoplasm with vimentin. (Right) Hybrid tumors (schwannoma with either neurofibroma or perineurioma) can be seen. This area shows a region of transition between a schwannoma and neurofibroma.

Neurofibroma With Wavy Nuclei



S100 Protein in Neurofibroma



(Left) The background collagenized stroma is noted in this neurofibroma. The spindle cells have wavy and elongated nuclei. Mast cells are frequently present. (Right) Nerve twigs  along with the Schwann cell proliferation are highlighted by the S100 protein immunohistochemistry. However, not all of the cells are positive, as the perineurites (perineurial cells) and fibroblasts are reactive with CD34, among other stains.

Leiomyoma and Smooth Muscle Tumors of Uncertain Malignant Potential

KEY FACTS

CLINICAL ISSUES

- Benign tumor of smooth muscle
- 1 of least common mesenchymal tumors in head and neck mucosal sites owing to
 - Relative paucity of smooth muscle in region other than related to blood vessels
- Thought to originate from smooth muscle within vascular structures (vascular leiomyoma)
- Presentation includes painless mass, nasal obstruction
- Complete surgical excision is curative
- Excellent prognosis; rarely recur

MACROSCOPIC

- On cut section, appears homogeneous with whorled appearance

MICROSCOPIC

- Interlacing bundles or fascicles of cells

- Blunt-ended or cigar-shaped nuclei, abundant eosinophilic cytoplasm
- **Cellular leiomyoma**
 - Increased cellularity, but absence of significant nuclear pleomorphism, increased mitotic activity, necrosis
- **Smooth muscle tumor of uncertain malignant potential**
 - Similar clinical features to leiomyoma
 - Increased cellularity
 - Moderate nuclear pleomorphism
 - Presence of no more than 4 mitoses per 10 HPFs
 - Locally infiltrative growth may occur

ANCILLARY TESTS

- **Positive:** Actins, vimentin, desmin

TOP DIFFERENTIAL DIAGNOSES

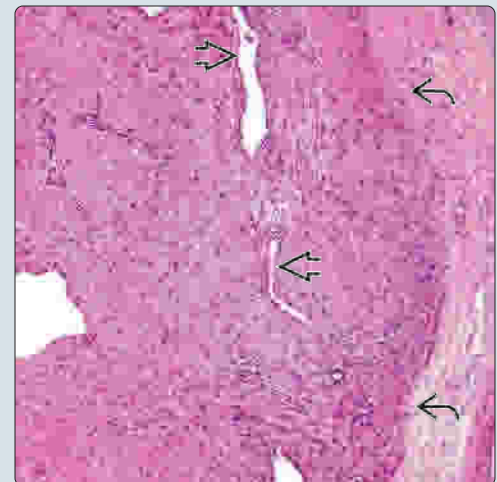
- Benign peripheral nerve sheath tumor, solitary fibrous tumor, leiomyosarcoma

Gross Image of Leiomyoma

(Left) On this cut section, the resected sinonasal leiomyoma shows characteristic macroscopic findings, including a tan-white color and whorled appearance. Histologically, this lesion was noteworthy for the presence of increased cellularity. (Right) The tumor seen here appears circumscribed to delineated [2], although it is not encapsulated and is composed of a spindle cell proliferation with fascicular growth. Lesional cells are intimately associated prominent vascular spaces [2].

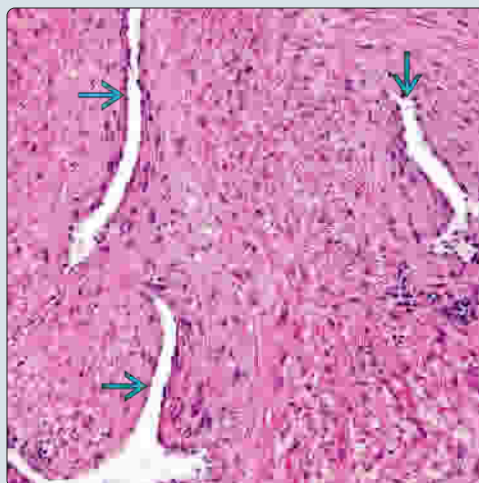


Vascular Leiomyoma



Large Vessels in Leiomyoma

(Left) The neoplastic cells seen here lie in continuity with endothelial-lined (slit-like) blood vessels [2], supporting the origin of sinonasal (and other mucosal-based) leiomyomas from smooth muscle cells of vascular walls, conferring the designation of vascular leiomyoma. (Right) At high magnification the lesional cells are composed of bland-appearing cigar-shaped nuclei with abundant eosinophilic cytoplasm. Intimate association with endothelial-lined (slit-like) vascular space is seen [2].



Sinonasal Leiomyoma



Leiomyoma and Smooth Muscle Tumors of Uncertain Malignant Potential

TERMINOLOGY

Abbreviations

- Smooth muscle tumor of uncertain malignant potential (SMTUMP)

Definitions

- Benign tumor of smooth muscle

ETIOLOGY/PATHOGENESIS

Idiopathic

- No known etiologic factors

CLINICAL ISSUES

Epidemiology

- Incidence
 - 1 of least common mesenchymal tumors in head and neck mucosal sites
 - Relative paucity of smooth muscle in region other than related to blood vessels
 - Thought to originate from smooth muscle within vascular structures (vascular leiomyoma)
- Age
 - All ages, but generally tumor of adult life
 - Peak incidence in 6th decade
- Sex
 - Male > female

Site

- Most common sites of occurrence in head and neck include
 - Skin and oral cavity (lips, tongue, and palate)
 - Sinonasal tract: Most often involves turbinates

Presentation

- Painless mass and nasal obstruction
- Other symptoms include dysphagia, voice changes, pain

Treatment

- Surgical approaches
 - Complete surgical excision is curative

Prognosis

- Excellent
- Rarely recur

MACROSCOPIC

General Features

- Solitary, well-demarcated, sessile submucosal lesion
- On cut section, appears homogeneous and tan-white with whorled appearance

Size

- Usually measures < 3 cm in diameter (may attain larger sizes)

MICROSCOPIC

Histologic Features

- Localized to submucosa, appears delineated, characterized by presence of interlacing bundles or fascicles of cells

- Blunt-ended or cigar-shaped nuclei with abundant eosinophilic cytoplasm
- Nuclei may appear epithelioid
- Nuclear palisading, perinuclear vacuolization may be seen
- No significant pleomorphism, mitotic activity, necrosis
- Neoplastic cells intimately associated with vascular spaces
- Degenerative-type changes may include stromal fibrosis, mucinous or myxoid alterations
- **Cellular leiomyoma**
 - Characterized by absolute increase in cells lacking significant pleomorphism, mitotic activity, necrosis
- SMTUMP
 - Similar clinical features to leiomyoma
 - Histologically characterized by
 - Increased cellularity
 - Moderate nuclear pleomorphism
 - Presence of no more than 4 mitoses per 10 HPFs
 - Locally infiltrative growth may occur

ANCILLARY TESTS

Histochemistry

- Masson trichrome: Cytoplasmic myofibrils appear red
- Phosphotungstic acid-hematoxylin: Cytoplasmic myofibrils appear blue

Immunohistochemistry

- **Positive:** Actins (smooth muscle and muscle specific), vimentin, desmin
- **Negative:** S100 protein, CD34, CD31
- Low proliferation rate (< 5%) by MIB-1 (Ki-67) staining

DIFFERENTIAL DIAGNOSIS

Benign Peripheral Nerve Sheath Tumors

- Diffuse S100 protein and SOX10 reactivity

Solitary Fibrous Tumor

- Characterized stromal collagenization ("ropey" collagen)
- Perivascular hyalinization, pericytic-type vasculature
- Presence of CD34 and STAT6 immunoreactivity

Leiomyosarcoma

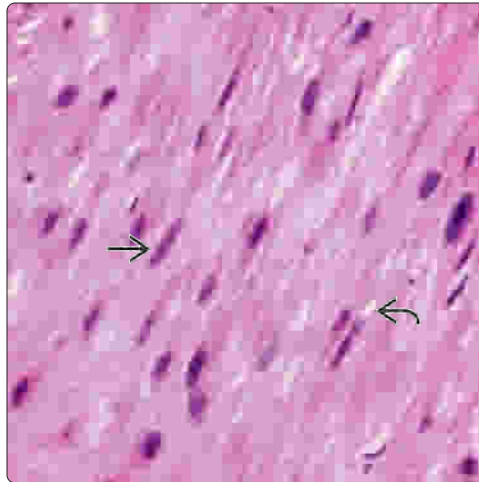
- Presence of increased cellularity with nuclear pleomorphism, ≥ 5 mitoses per 10 HPFs, and infiltrative growth

SELECTED REFERENCES

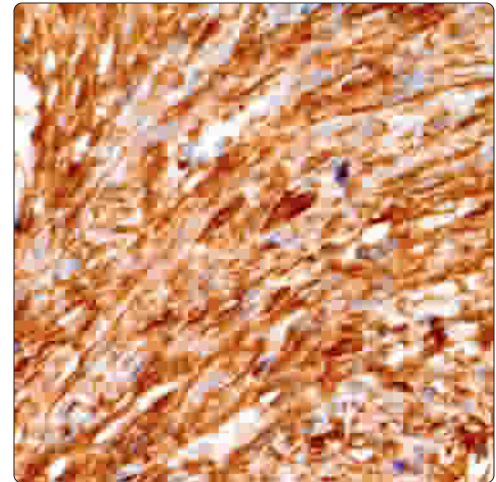
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Fascicular Pattern

(Left) At high magnification the lesional cells include the presence of blunt-ended or cigar-shaped nuclei with eosinophilic cytoplasm, as well as perinuclear vacuolization. There is an absence of significant nuclear pleomorphism and increased mitotic activity. (Right) The myogenic nature of the lesional cells is confirmed by the presence of diffuse and strong reactivity for smooth muscle actin (SMA) immunoreactivity.

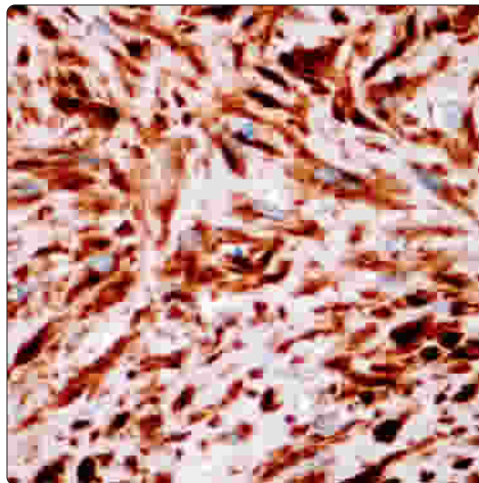


Diffuse SMA Reaction

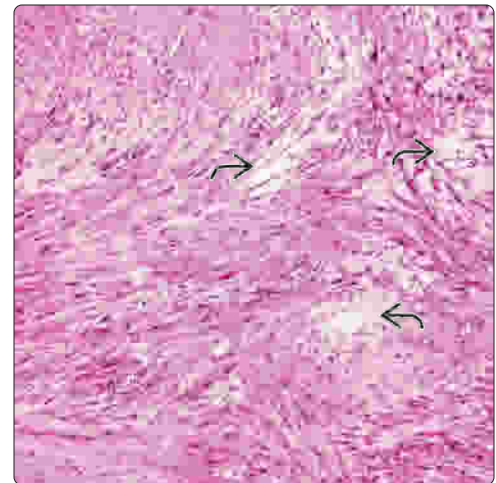


Strong Desmin Reaction

(Left) In addition to actin staining, lesional cells may be diffusely reactive for desmin. The light microscopic features coupled with immunoreactivity for myogenic markers allows differentiation from benign peripheral nerve sheath tumors (e.g., schwannoma) and solitary fibrous tumor. (Right) In this example of a sinonasal leiomyoma, the neoplastic proliferation shows fascicular growth between which there are myxoid/mucinous foci representing associated degenerative changes.

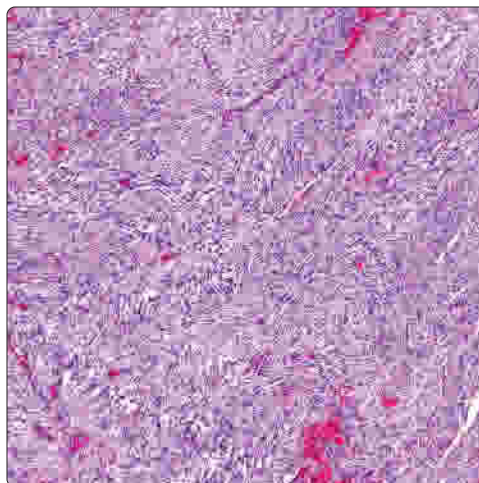


Sinonasal Leiomyoma With Degenerative Changes

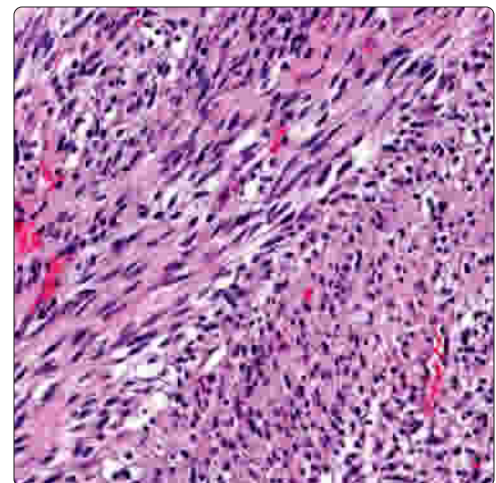


Fascicles in Cellular Leiomyoma

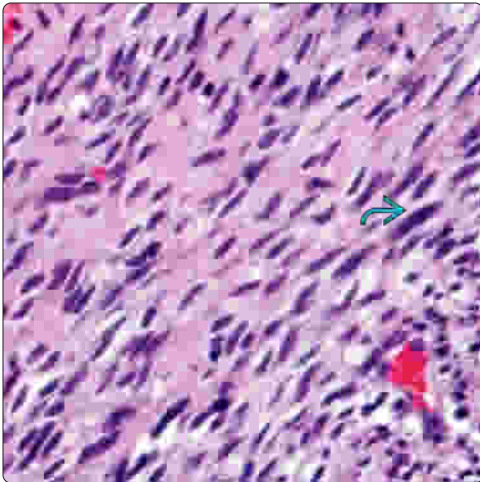
(Left) In comparison to "conventional" leiomyomas, cellular leiomyomas show increased cellularity but retain a characteristic fascicular growth composed of interlacing bundles of neoplastic cells. Lesional cells are associated with slit-like blood vessels supporting the origin of tumor from vascular spaces. (Right) Similar to its less cellular component, there is fascicular growth composed of interlacing bundles of neoplastic cells that, in spite of increased cellularity, lacks features diagnostic for a leiomyosarcoma.



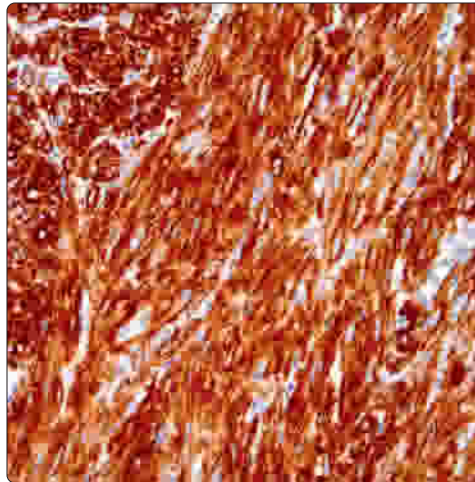
Sinonasal Cellular Leiomyoma



Bland Nuclei in Cellular Leiomyoma

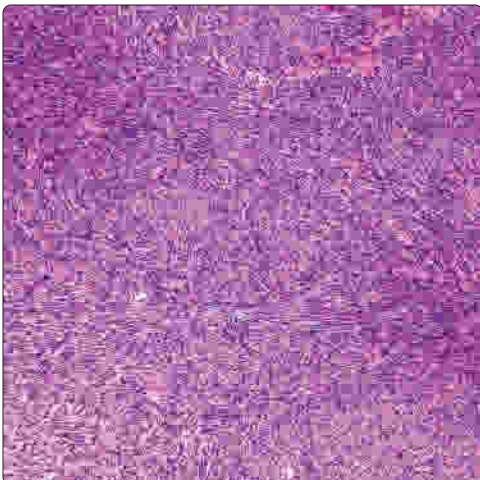


SMA Reaction in Cellular Leiomyoma

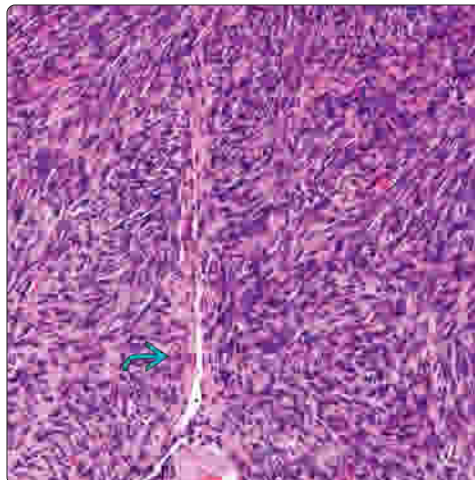


(Left) In spite of the increased cellularity, there is no significant nuclear pleomorphism and no substantial increase in the mitotic activity and absence of necrosis. Scattered enlarged hyperchromatic nuclei are seen [\[2\]](#). (Right) There is diffuse and strong immunoreactivity for SMA seen here. Other than the increased cellularity, the overall findings are those of a leiomyoma, albeit a cellular one, without evidence to support the diagnosis of a leiomyosarcoma.

High Cellularity in SMTUMP

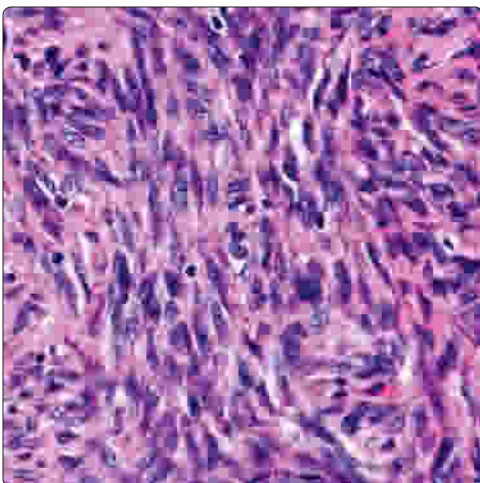


Vascular Origin of SMTUMP

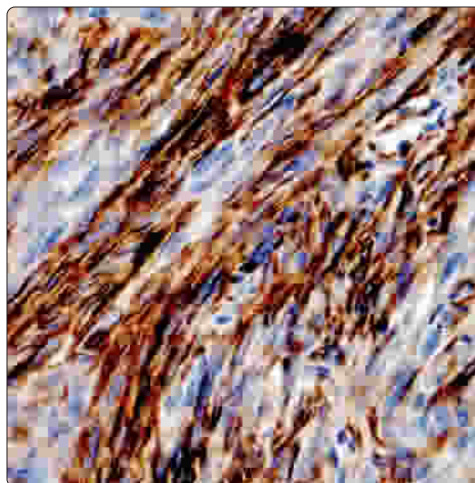


(Left) Sinonasal smooth muscle tumor of uncertain malignant potential (SMTUMP) shows fascicular to storiform growth with marked increase in cellularity. This tumor was located in the submucosa and revealed focally infiltrative growth (not shown). (Right) Similar to sinonasal leiomyomas, SMTUMPs of the sinonasal tract likely arise from the smooth muscle in the wall of vascular spaces, accounting for the intimate association of the neoplasm with (sinonasal) blood vessels [\[2\]](#).

Moderate Pleomorphism in SMTUMP



SMA Reaction in SMTUMP



(Left) In contrast to cellular leiomyomas, the cellular component of SMTUMP reveals moderate nuclear pleomorphism and increased mitotic activity (not shown); however, the mitotic rate does not exceed 4 mitoses per 10 HPFs. (Right) SMTUMP shows diffuse and strong immunoreactivity for SMA. SMTUMP may show locally infiltrative growth, but the absence of significant increase in mitotic activity (≥ 4 mitoses per 10 HPFs) allows differentiation from leiomyosarcoma.

Fibromatosis/Desmoid-Type Fibromatosis

KEY FACTS

TERMINOLOGY

- Locally aggressive, intermediate type of nonmetastasizing, well-differentiated, unencapsulated monoclonal myofibroblastic proliferation with tendency for local invasion and recurrence

CLINICAL ISSUES

- 0.2-0.4 per 100,000, with ~ 15% within head and neck
- Mean: 18 years for all head and neck sites
- Male > female (1.1:1)
- Maxillary sinus and turbinates in sinonasal tract, but mandible most commonly affected head and neck site
- Local but complete surgical excision; there are frequently positive margins

MICROSCOPIC

- Infiltrative growth with low to moderate cellularity

- Broad fascicles of bland-looking spindle cells arranged in uniform direction ("purposeful") with elongated parallel blood vessels
- Spindle cells have myofibroblastic appearance, with low nuclear:cytoplasmic ratio and uniformly bland ovoid nuclei with indistinct nucleoli
- Matrix is collagenized to focally myxoid; keloid-like collagen may be present


ANCILLARY TESTS

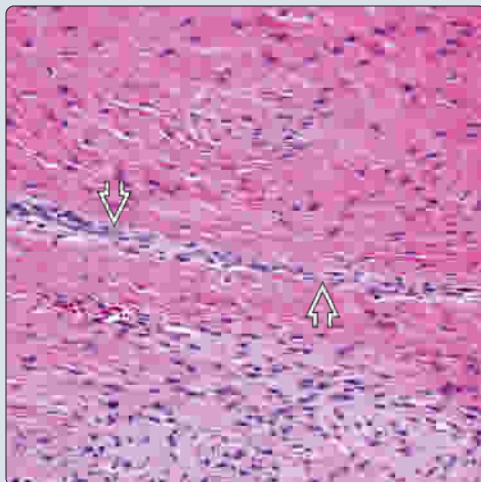
- Positive:** β -catenin (nuclear), actins, vimentin; focal desmin
- Somatic** mutations in β -catenin (*CTNNB1*) gene on 3p21

TOP DIFFERENTIAL DIAGNOSES

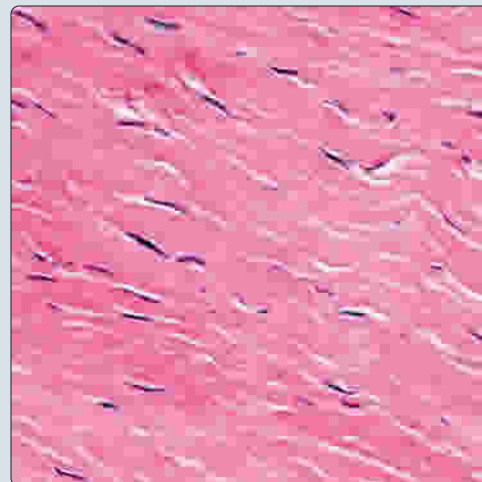
- Ossifying fibroma, solitary fibrous tumor, hypertrophic scar, juvenile ossifying fibroma, glomangiopericytoma, perineurioma, chondromyxoid fibroma

Elongated Vessels and Spindle Cells


(Left) Hematoxylin and eosin shows a parallel arrangement of elongated blood vessels  to the bland spindle cell population. There is a slight variation in cellularity. (Right) Hematoxylin and eosin shows broad fascicles of bland-looking spindle cells arranged in the same direction. Note the very heavy collagen deposition. There are usually no mitotic figures or pleomorphism.

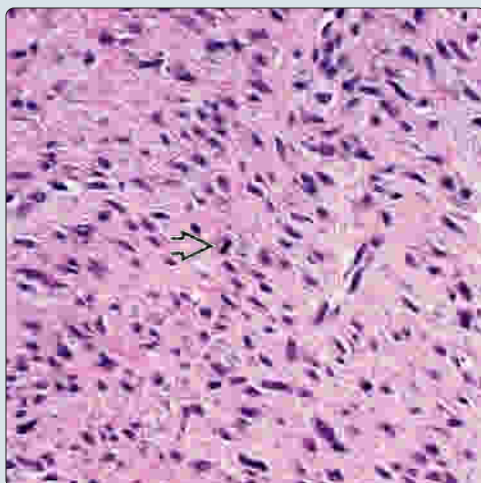
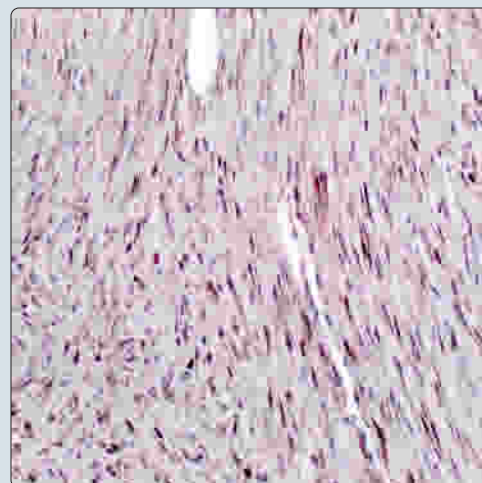


Heavy Collagenization



Myofibroblastic Spindled Cells

(Left) The spindle cells have a myofibroblastic appearance, with low nuclear:cytoplasmic ratio and uniformly bland ovoid nuclei. Note the single mitotic figure , an uncommon finding (it is not atypical). (Right) There is a strong and diffuse nuclear reaction with β -catenin in the lesional cells in this example of a desmoid. The reaction is quite helpful in the differential diagnosis.

Strong, Diffuse Nuclear β -Catenin Reaction

TERMINOLOGY

Synonyms

- Desmoid tumor, extraabdominal desmoid

Definitions

- Locally aggressive, intermediate type of nonmetastasizing, well-differentiated, unencapsulated monoclonal myofibroblastic proliferation with tendency for local invasion and recurrence
 - Intermediate between fibroma and fibrosarcoma

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Hyperestrogenism during pregnancy, trauma, and surgery have been suggested

CLINICAL ISSUES

Epidemiology

- Incidence
 - 0.2-0.4 per 100,000, with ~ 15% within head and neck
- Age
 - All ages affected but more frequent in young people
 - Mean: 18 years for all head and neck sites
- Sex
 - Male > female (1.1:1)

Site

- Maxillary sinus and turbinates in sinonasal tract (SNT), but mandible most commonly affected head and neck site
- Nasal cavity, other paranasal sinuses, and nasopharynx are rarely affected

Presentation

- Nonspecific signs and symptoms
 - Nasal obstruction, epistaxis, mass, facial pain, tooth displacement
- Bilateral disease in ~ 25%
- Rarely, associated with familial adenomatous polyposis (FAP) or Gardner syndrome

Treatment

- Local but complete surgical excision; there are frequently positive margins
- Treatment with receptor tyrosine kinase inhibition shows promise

Prognosis

- Excellent without morbidity of other anatomic sites
- Recurrence/residual disease in ~ 25% of patients
- No metastases for sinonasal and nasopharynx lesions

MACROSCOPIC

General Features

- Tan-white, glistening, and rubbery firm mass, polypoid and often infiltrative
- May be multicentric (especially in Gardner syndrome)

Size

- Usually small; nasopharyngeal tumors are larger (up to 7 cm)

MICROSCOPIC

Histologic Features

- Infiltrative growth with low to moderate cellularity
- Broad fascicles of bland-looking spindle cells arranged in uniform direction ("purposeful")
- Elongated blood vessels are frequently observed running parallel to each other
- Spindle cells have myofibroblastic appearance, with low nuclear:cytoplasmic ratio and uniformly bland ovoid nuclei with indistinct nucleoli
- Mitotic figures are infrequent and never atypical
- Matrix is collagenized to focally myxoid; keloid-like collagen may be present

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** β -catenin (nuclear), actins, vimentin; focal desmin

Genetic Testing

- **Somatic** mutations in β -catenin (*CTNNB1*) gene on 3p21 in most cases
 - Results in activation of Wnt/catenin signaling pathway
- FAP has inactivating **germline** mutations in adenomatous polyposis coli (*APC*) gene on 5q21-q22

DIFFERENTIAL DIAGNOSIS

Solitary Fibrous Tumor

- Wavy spindle nuclei with ropy collagen
- **Positive:** STAT6, CD34, Bcl-2; **negative:** β -catenin

Glomangiopericytoma

- Cellular with patternless appearance, perivascular hyalinization; background eosinophils and mast cells
- **Positive:** β -catenin, SMA, MSA

Perineurioma

- Spindle cell tumor arranged in many patterns, whorled to concentrically stratified, with bland bipolar cells with thin cytoplasmic processes
- **Positive:** EMA, claudin-1, GLUT1, CD34; **negative:** β -catenin

Ossifying Fibroma (Including Juvenile Active)

- Bony, calcified, or psammomatoid ossicles within swirled, cellular stromal growth, lacking collagen

Hypertrophic Scar

- Heavy collagen deposition, lacking purposeful vessels

Chondromyxoid Fibroma

- Myxoid or chondroid matrix; fibrous connective tissue

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Solitary Fibrous Tumor

KEY FACTS

TERMINOLOGY

- Mesenchymal tumor of probable fibroblastic type identical to pleural solitary fibrous tumors (SFTs)

CLINICAL ISSUES

- Range: 20-80 years; median: 50 years
- Equal gender distribution
- Nonspecific findings are common (headaches)
- Painless, unilateral, slow-growing mass
- Complete, but conservative local excision with clear margins
- Overall, excellent long-term prognosis

MACROSCOPIC

- Usually polypoid and firm, well circumscribed, but partially encapsulated
- Mean: 2.5 cm; range: 1-6 cm

MICROSCOPIC


- Requires combination of architectural, cytomorphologic, and immunophenotypic features as diagnosis of exclusion
- Unencapsulated proliferation of bland, blunt, spindle-shaped cells in patternless growth of alternating hypo- and hypercellular areas
- Syncytial cells are separated by thick bands of ropy keloidal collagen bundles
- Hemangiopericytoma-like vascular pattern can be seen

ANCILLARY TESTS

- Characteristically, CD34, Bcl-2, STAT6 (nuclear), and CD99 immunoreactive

TOP DIFFERENTIAL DIAGNOSES

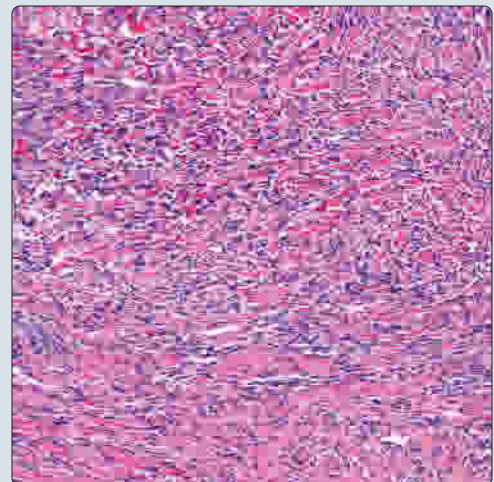
- Sinonasal glomangiopericytoma, fibrosarcoma, synovial sarcoma, biphenotypic sinonasal sarcoma, schwannoma, leiomyoma, meningioma



(Left) The respiratory epithelium is intact , subtended by a cellular proliferation of a patternless spindle cell population with associated collagen deposition. Small vessels are noted. **(Right)** This tumor is arranged in a patternless pattern of spindled tumor cells set within very well-developed keloid-like collagen bundles. This is a characteristic histologic appearance.

Intact Surface Over Spindled Proliferation

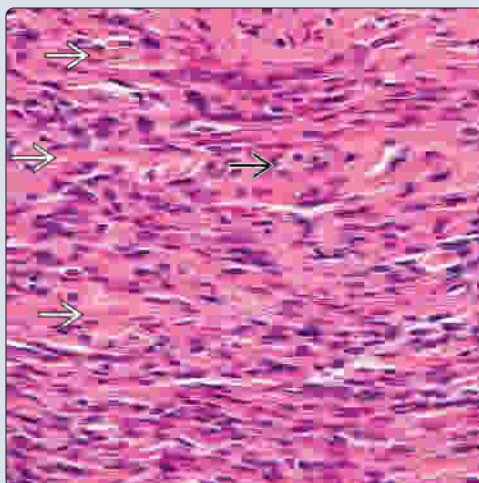


Patternless Proliferation With Collagen

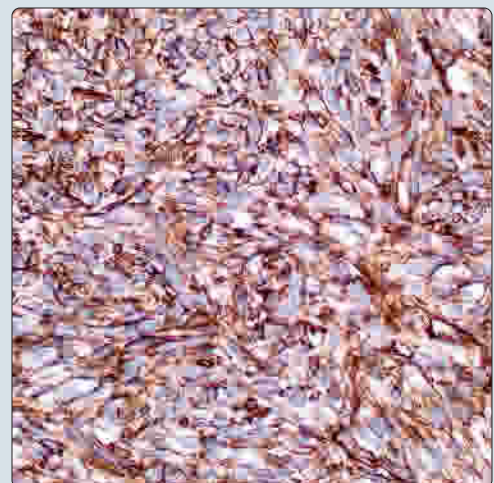


(Left) Hematoxylin and eosin shows a spindle cell proliferation arranged in a patternless growth of hypercellular areas with isolated blood vessels . Note the ropy eosinophilic  collagen deposition. **(Right)** Nearly all of the neoplastic cells in this field show a strong and diffuse reaction with CD34. CD34 is also seen in other tumors in the differential diagnosis, and so must be interpreted in light of the H&E findings.

High Power of Bland Spindled Cells



Strong Cytoplasmic CD34 Reaction



TERMINOLOGY**Abbreviations**

- Solitary fibrous tumor (SFT)

Synonyms

- Hemangiopericytoma
 - SFT to hemangiopericytoma is considered morphologic continuum
 - However, this is not the same as **glomangiopericytoma**, considered unique tumor entity in sinonasal tract

Definitions

- Mesenchymal tumor of probable fibroblastic type identical to pleural SFTs

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Very rare (< 0.1% of all sinonasal tract neoplasms)
- Age
 - Range: 20-80 years; median: 50 years
 - Rare in children and adolescents
- Sex
 - Equal gender distribution

Site

- Anywhere in sinonasal tract
 - Orbit (direct extension from meninges) > maxillary sinus > sphenoid-ethmoid sinuses > nasal cavity (direct extension from sinuses) > oral cavity > nasopharynx

Presentation

- Nonspecific findings are common (headaches)
- Painless, unilateral, slow-growing mass
- Obstructive symptoms, epistaxis, rhinorrhea
- Paraneoplastic syndrome (hypoglycemia due to secretion of insulin-like growth factor) has been reported

Treatment

- Complete but conservative local excision with clear margins
 - Endoscopic sinus surgery can work well (monobloc excision)

Prognosis

- Overall, excellent long-term prognosis
- Majority are benign, but behavior is unpredictable, not necessarily based on histologic parameters
 - Therefore, long-term clinical follow-up is advocated
- Infrequently, recurrences will develop (< 10%)
- Rare cases (< 2%) may have malignant behavior, based on increased tumor size, atypical mitotic figures, necrosis
 - If metastases develop, lungs, bone, and liver are most frequently affected

IMAGING**General Features**

- CT images show well-circumscribed tumors that strongly enhance with contrast, with bone remodeling
- Tumors show enhancement with gadolinium contrast on T1-weighted MR images

MACROSCOPIC**General Features**

- Usually polypoid and firm
- Well circumscribed, but partially encapsulated
- Multinodular, whitish cut surface, although myxoid and hemorrhagic areas can be observed

Size

- Mean: 2.5 cm; range: 1-6 cm
 - Size may be constrained due to anatomic confines

MICROSCOPIC**Histologic Features**

- Diagnosis rests on combination of architectural, cytomorphologic, and immunophenotypic features
- Separated into benign and malignant forms
- Nonencapsulated mass below intact, uninvolved respiratory epithelium
- Patternless growth of variably cellular, alternating hypo- and hypercellular areas
 - Hemangiopericytoma-like vascular pattern can be seen
- Proliferation of bland, blunt, spindle-shaped cells, often syncytial in appearance
- Round to spindle-shaped cells with indistinct borders
- Cells are separated by thick bands of ropy keloidal or hyalinized collagen bundles
- Neoplastic cells are intersected by thin-walled vascular spaces
 - Vessels are sometimes patulous or hemangiopericytoma-like
- Myxoid change, areas of fibrosis, and interstitial mast cells may be present
- Mitoses are uncommon
- Fat deposition and giant cells are exceedingly uncommon in sinonasal tract cases
- Malignant SFT is very rare
 - Infiltrative borders, high cellularity, pleomorphism, tumor necrosis, increased mitotic figures

Margins

- Positive margins tend to be associated with recurrences

ANCILLARY TESTS**Immunohistochemistry**

- Characteristically, CD34, Bcl-2, STAT6 (nuclear) and CD99 immunoreactive

Flow Cytometry

- Most tumors are diploid, but seldom evaluated

Genetic Testing

- *NAB2-STAT6* fusion (inv12(q13q13))
- Cytogenetics are heterogeneous, but abnormalities tend to increase in larger tumors

Electron Microscopy

- Primitive myofibroblastic or fibroblast-like cells
- Ultrastructural features are usually nonspecific in SFT

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CD34	Positive	Cytoplasmic	Strong and diffuse in neoplastic cells
Bcl-2	Positive	Cytoplasmic	Strong in most neoplastic cells
CD99	Positive	Cytoplasmic	Many tumor cells will be positive
STAT6	Positive	Nuclear	Most tumor cells show strong reaction
Vimentin	Positive	Cytoplasmic	Strong and diffuse in neoplastic cells
Actin-sm	Positive	Cytoplasmic	Weak, < 25% of cells reactive
Actin-HHF-35	Positive	Cytoplasmic	Isolated, rare cells may be positive
EMA	Positive	Cell membrane & cytoplasm	Weak, < 25% of cells reactive
GFAP	Positive	Cytoplasmic	Isolated, rare cells may be positive
Ki-67	Positive	Nuclear	< 3-5% of nuclei
CK-PAN	Negative		
β-catenin	Negative		No nuclear reaction, although cytoplasmic reaction can be seen
Calretinin	Negative		
S100	Negative		
HBME-1	Negative		

DIFFERENTIAL DIAGNOSIS

Sinonasal Glomangiopericytoma

- Ovoid cells in syncytium with prominent, often patulous vessels seen throughout
- Perivascular hyalinization nearly pathognomonic
- Eosinophils, mast cells, and extravasated erythrocytes
- **Positive:** SMA, MSA, β-catenin (nuclear); **negative:** CD34, Bcl-2, CD99, STAT6

Fibrosarcoma

- Highly cellular, with tumor cells arranged in short, interlacing fascicles
- Mitotic figures are easily identified, and sometimes necrosis
- **Positive:** Vimentin only (strong, diffuse)

Synovial Sarcoma

- Frequently biphasic tumor, highly cellular, arranged in short interlacing fascicles, with glandular profiles in biphasic types
- **Positive:** EMA, cytokeratin, TLE1, Bcl-2
- Characteristic and unique cytogenetics: t(X;18)(p11.2;q11.2) translocation resulting in *SSX1-SS18* fusion transcript

Biphenotypic Sinonasal Sarcoma

- Epithelial inclusions and fascicular architecture, but often with destructive growth (bone included)
- **Positive:** S100 protein, SMA, MSA, CD34 (focal); **negative:** STAT6 (nuclear)

Schwannoma

- Alternating hyper- and hypocellular areas with palisading and perivascular hyalinization
 - Antoni A areas are more common in sinonasal tumors
- Wavy nuclei with elongated nuclear extensions
- Lacks keloid-like collagen deposition
- **Positive:** S100 protein, SOX10; **negative:** CD34, Bcl-2, SMA

Leiomyoma

- Rare in sinonasal tract; cellular tumors with short interlacing fascicles of blunt spindled cells with spindle nuclei
- **Positive:** SMA, MSA, desmin; **negative:** CD34

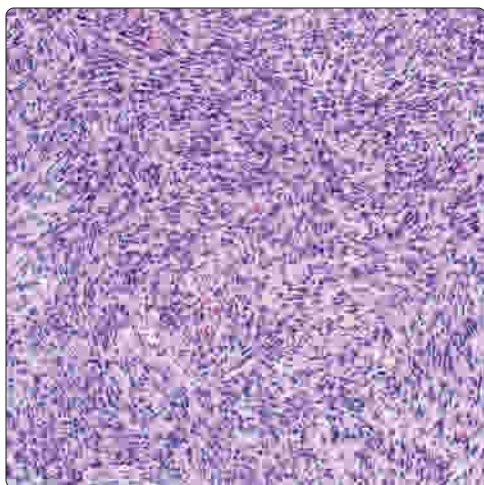
Meningioma

- Fibroblastic or meningothelial variant shows spindle-shaped cells in fascicles, associated with variable collagen deposition, and sometimes linear stromal calcifications
- **Positive:** EMA, CK7, progesterone; **negative:** CD34, Bcl-2

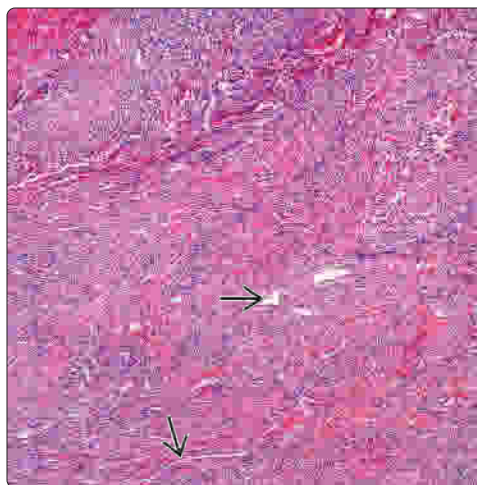
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Patternless Pattern

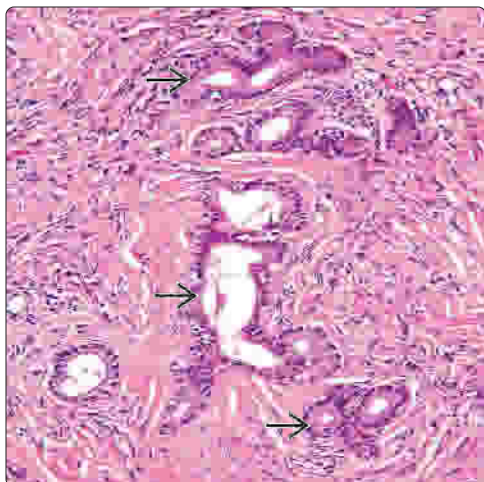


Stromal Keloid-Like Collagen

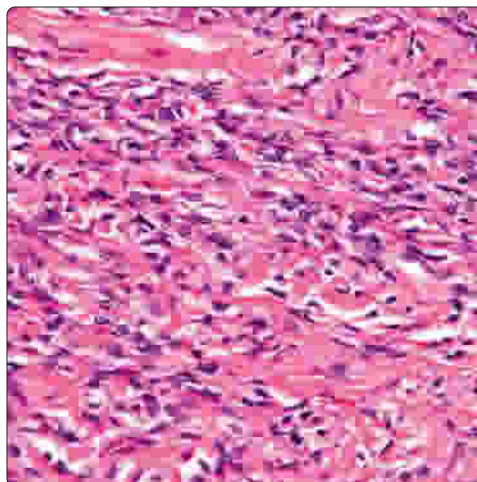



(Left) There are sheets and short fascicles interlaced in this solitary fibrous tumor (SFT). Note that there is limited to absent keloid-like collagen in this tumor. **(Right)** There is a heavy deposition of wiry, keloid-like collagen in this SFT. A number of open, patulous vessels  are seen within the spindled cell proliferation, a characteristic feature of this tumor.

Entrapped Minor Mucoserous Glands

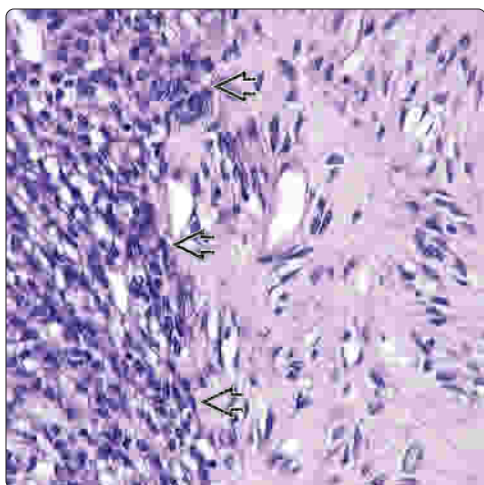


Eosinophilic Keloid-Like Collagen Bundles

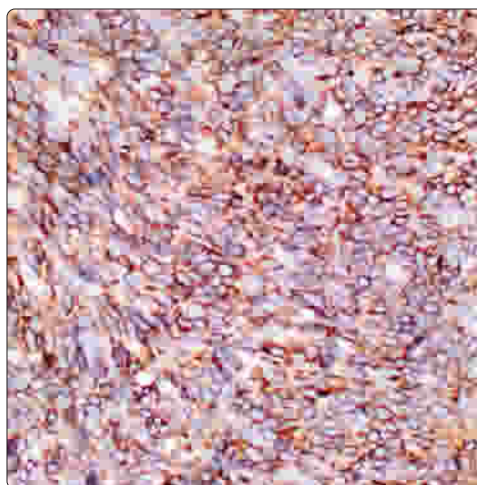



(Left) Hematoxylin and eosin demonstrates entrapment of the minor mucoserous glands . The proliferation surrounds these glands, but does not destroy them. There is a haphazard distribution to the proliferation, with heavy keloid-like collagen deposition. **(Right)** Cells are separated by thick bands of ropy keloidal collagen bundles, brightly eosinophilic with hematoxylin and eosin stain. There is a waviness to the proliferation, with elongated, blunt, spindle-shaped nuclei.

SFT Combined With Glomangiopericytoma



Bcl-2 Highlights Neoplastic Cells



(Left) This is an example of a collision tumor. The left side highlights the findings of a glomangiopericytoma  with a high cellularity and a lack of collagen deposition, while the right side shows the characteristic findings of a solitary fibrous tumor. Collision tumors are rare. **(Right)** Nearly all of the neoplastic cells show a strong and diffuse cytoplasmic reaction with Bcl-2. This marker is not unique to SFT, but is also seen in other tumors in the differential diagnosis.

Myxoma/Fibromyxoma

KEY FACTS

TERMINOLOGY

- Benign neoplasm of uncertain histogenesis characterized by bland-appearing spindle to stellate cells set in myxoid to fibromyxoid stroma
- 2 forms identified in head and neck
 - Facial skeletal derived
 - Soft tissue derived

CLINICAL ISSUES

- Gnathic sites more common than extragnathic sites
 - Mandible > maxilla
- Extragnathic tumors primarily involve sinonasal tract
- Painless swelling of affected area
- Slow growing, usually follows benign course
- Wide local excision treatment of choice
- Locally recur following inadequate excision
 - May show invasive growth


MICROSCOPIC

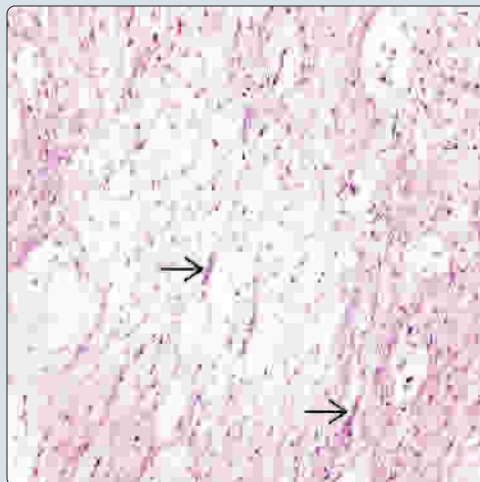
- Histology is same, irrespective of site/setting of occurrence
 - Scant, loosely cellular proliferation of spindle-shaped or stellate-appearing cells embedded in abundant mucinous stroma
 - Small, hyperchromatic nuclei with absence of cellular pleomorphism, mitotic figures, and necrosis
 - Amount of collagenous fibrillary stroma may vary and depending on extent may confer term fibromyxoma
 - Periphery appears circumscribed, but local infiltration may be present
 - Vascular component present but limited in extent with absence of delicate plexiform capillary vascular network, a finding that can be seen in various sarcomas

ANCILLARY TESTS

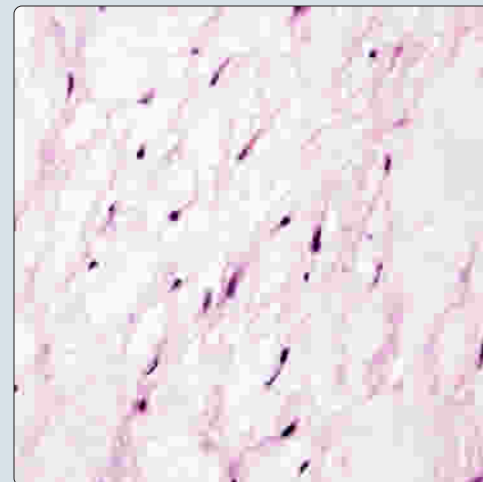
- **Negative:** S100 protein, MUC4, β -catenin, CD34, STAT6
- **Positive:** Vimentin

Sinonasal Myxoma



(Left) Sinonasal myxoma is characterized by the presence of relatively hypocellular spindle-shaped cellular proliferation set in a prominent myxoid stroma. The vascular component is scant but identifiable . **(Right)** Loosely cellular proliferation comprised of spindle-shaped to stellate-appearing cells is shown set in a myxomatous-appearing stroma. The cells lack significant nuclear pleomorphism and increased mitotic activity, and there is an absence of arborizing capillary vasculature that can be seen in sarcomas.

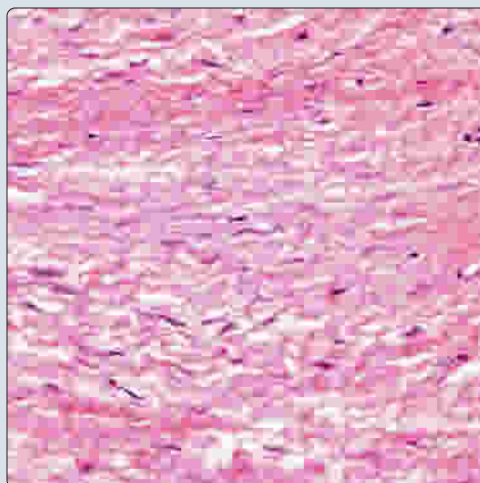


Sinonasal Myxoma

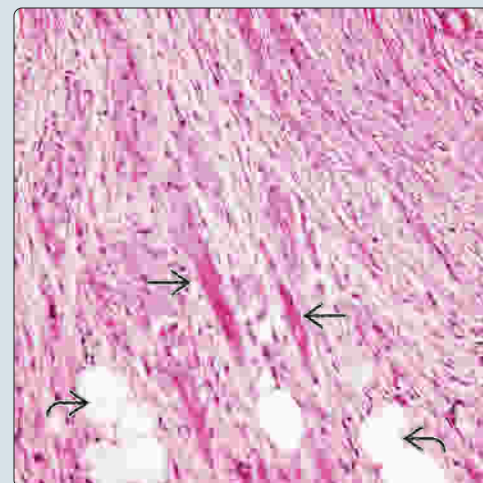


Sinonasal Fibromyxoma

(Left) The presence of increased collagenous fibrillary stroma would confer the designation of fibromyxoma. Other than the stromal component, the cellularity and cytomorphic features are similar to myxomas. **(Right)** Lesional cells may infiltrate into soft tissues (skeletal muscle , fat ) at the periphery of the lesion, creating difficulties in assuring complete surgical resection, potentially resulting in local recurrent tumor.



Sinonasal Fibromyxoma



TERMINOLOGY

Definitions

- Benign neoplasm of uncertain histogenesis characterized by bland-appearing spindle to stellate cells set in myxoid to fibromyxoid stroma
 - 2 forms identified in head and neck
 - Facial skeletal derived
 - Soft tissue derived

ETIOLOGY/PATHOGENESIS

Idiopathic

- No known etiologic factors

Developmental

- Localization to jaw bones suggests origin from primordial odontogenic mesenchyme or osteogenic embryonic connective tissue
- Sinonasal tract tumors appear to be of osseous derivation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare
- Age
 - Occurs over wide range
 - Facial-skeleton: Most frequent in 2nd and 3rd decades
- Sex
 - Equal gender distribution

Site

- **Facial skeleton-derived**
 - Gnathic sites
 - Mandible (posterior and condylar regions) > maxilla (zygomatic process and alveolar bone)
 - Extragnathic tumors
 - Primarily involve sinonasal tract
 - Maxillary sinus (antrum) most often involved with secondary extension into nasal cavity
 - Extension to orbit and cranial cavity may occur
- **Soft tissue-derived**
 - In head and neck, common sites include paraoral soft tissues, pharynx, larynx, parotid gland, tonsil/ear
 - Mazabraud syndrome refers to association between soft tissue myxomas and fibrous dysplasia
 - Multiple myxomas present; tend to be intramuscular; majority have polyostotic fibrous dysplasia
 - Patients may suffer from McCune-Albright syndrome
 - Carney complex
 - Autosomal dominant syndrome of myxomas (cardiac, other soft tissue sites including intraoral, ear), spotty pigmentation and endocrine overactivity

Presentation

- Painless swelling of affected area

Treatment

- Surgical approaches
 - Wide local excision treatment of choice

Prognosis

- Slow growing, usually follows benign course
 - Potential for local recurrence with destructive growth following inadequate excision
- Presence of metastasis should seriously question benign diagnosis; probably represents sarcoma

MACROSCOPIC

General Features

- Delineated but unencapsulated lesion, multinodular, rubbery to firm, tan-yellow with gelatinous appearance

MICROSCOPIC

Histologic Features

- Histology is same, irrespective of site/setting of occurrence
 - Scant, loosely cellular proliferation of spindle-shaped or stellate-appearing cells embedded in abundant mucinous stroma
 - Small, hyperchromatic nuclei with absence of cellular pleomorphism, mitotic figures, and necrosis
 - Amount of collagenous fibrillary stroma may vary and depending on extent may confer term fibromyxoma
 - Periphery appears circumscribed, but local infiltration may be present
 - Relative paucity of inflammatory cells
- Vascular component present but limited in extent with absence of delicate plexiform capillary vascular network, a finding that can be seen in various sarcomas
- Intraoral lesions may include odontogenic epithelium representing odontogenic myxoma

ANCILLARY TESTS

Histochemistry

- Mucinous stroma stains with acid mucopolysaccharides
- In general, special stains are of limited diagnostic utility

Immunohistochemistry

- **Positive:** Vimentin; **negative:** S100 protein, MUC4, β -catenin, CD34, STAT6

DIFFERENTIAL DIAGNOSIS

Sinonasal Inflammatory Polyps

- Abundant mixed inflammatory cells
- Edematous rather than mucinous stromal changes

Sarcomas With Myxoid Component

- Increased cellularity, pleomorphism, presence of delicate arborizing capillary vasculature

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KEY FACTS

TERMINOLOGY

- Soft tissue tumor showing perivascular myoid differentiation

CLINICAL ISSUES

- Nasal cavity is usually affected in isolation
- Present with nasal obstruction, mass, polyps, sinusitis, difficulty breathing, and epistaxis
- Female > male (1.2:1)
- Excellent long-term outcome with surgery alone, although recurrences develop (~ 27%)

MACROSCOPIC

- Tends to be polypoid mass ~ 3 cm

MICROSCOPIC

- Surface epithelium usually intact (respiratory-type or metaplastic squamous mucosa)
- Peritheliomatous (perivascular) hyalinization is characteristic

- Cellular, diffuse, syncytial arrangement
- Many patterns of growth, often within same tumor
- Ramifying, branching pattern of vessels
- Mixture of inflammatory cells in background
 - Eosinophils, mast cells, and lymphocytes, although first 2 predominate
- Extravasated erythrocytes

ANCILLARY TESTS

- Shows myoid phenotype (actins positive); β -catenin (nuclear and cytoplasmic) and cyclin D1 (nuclear)
- Lacks vascular markers (CD34, CD31, FVIIIIRAg)
- *CTNNB1* mutations with β -catenin oncogenic activation

TOP DIFFERENTIAL DIAGNOSES

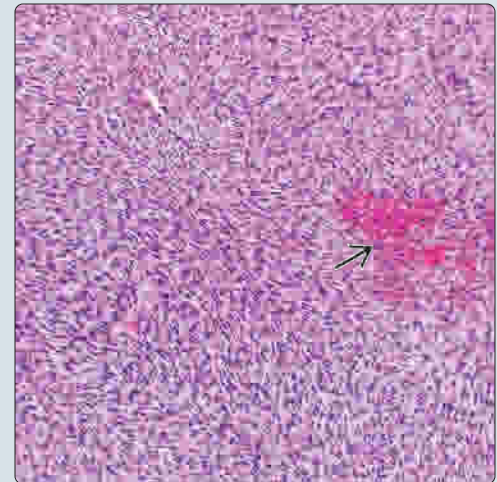
- Leiomyoma, schwannoma, solitary fibrous tumor, fibrosarcoma, meningioma
- Lobular capillary hemangioma, nasopharyngeal angiofibroma

Patternless Pattern of Glomangiopericytoma

(Left) The surface epithelium is intact . There is a patternless pattern below the surface showing a syncytial arrangement with thin-walled vessels. (Right) There is a vague short fascicular arrangement to this spindled cell proliferation. The cells are arranged in a syncytium, focally showing extravasated erythrocytes .

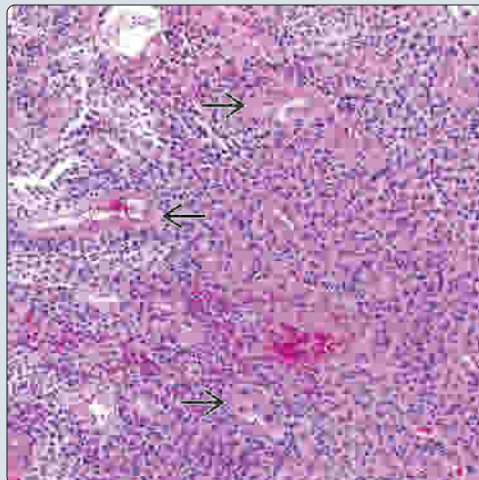


Syncytium of Spindled Cells

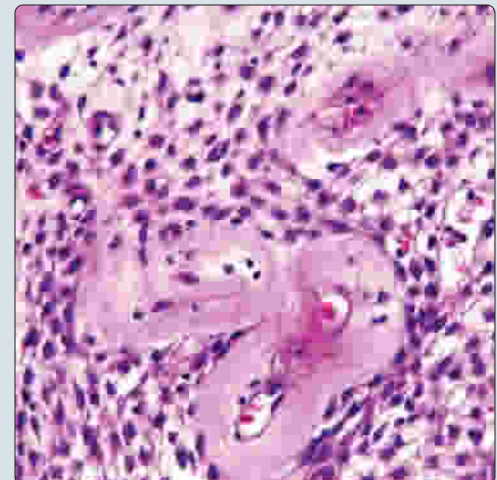


Peritheliomatous Hyalinization

(Left) Glomangiopericytoma shows a cellular, syncytial arrangement of cells that are always associated with a rich vascular compartment. The vessels are branching or staghorn-like with peritheliomatous hyalinization . (Right) The strong, heavy, perivascular (peritheliomatous) hyalinization is quite characteristic for this tumor in the setting of a monotonous proliferation. The neoplasm is bland and arranged in a syncytium.



Marked Peritheliomatous Hyalinization



TERMINOLOGY

Synonyms

- Sinonasal-type hemangiopericytoma (SNTHPC) (previous name)
- Glomus tumor
- Intranasal myopericytoma

Definitions

- Soft tissue tumor showing perivascular myoid differentiation defined by glomus (myoid) and hemangiopericytoma (pericyte) features within same lesion

ETIOLOGY/PATHOGENESIS

Myopericyte

- May arise from plentiful pericytes associated with vessels of nasal cavity

CTNNB1 Mutations

- Mutational activation of β -catenin and associated cyclin D1 overexpression

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare, comprising < 0.5% of sinonasal primary neoplasms
- Age
 - Broad range at presentation (5-90 years old); mean in 7th decade
 - Age at presentation does not affect prognosis
- Sex
 - Female > male (1.2:1)
 - No difference in outcome based on gender

Site

- Nasal cavity is usually affected in isolation
 - Turbinate and septum are occasionally affected in isolation
- Maxillary and ethmoid sinuses may also be affected in conjunction with nasal cavity
- Bilateral tumors are uncommon (~ 5%)

Presentation

- Nasal obstruction, mass, polyps, difficulty breathing
- Sinusitis, discharge, changes in smell
- Epistaxis is uncommon
- Headache, congestion, pain
- Symptoms usually present for < 1 year
- Rare association with oncogenic osteomalacia
 - Serum hypophosphatemia, elevated alkaline phosphatase, normal serum calcium and parathyroid hormone levels

Treatment

- Options, risks, complications
 - Surgery is treatment of choice, although radiation has been used in nonsurgical candidates
- Surgical approaches
 - Polypectomy or wide surgical excision
 - Complete surgical extirpation decreases risk of recurrence

Prognosis

- Excellent long-term survival (5-year survival ~ 90%)
- Recurrences may develop (~ 27%)
 - Multiple recurrences may be seen
- Recurrences are associated with long duration of symptoms, bone invasion, and profound nuclear pleomorphism
- Long-term clinical follow-up advocated as recurrences may develop late

IMAGING

CT Findings

- Destructive polypoid mass of nasal cavity (paranasal sinuses) accompanied by bone erosion or sclerosis

MACROSCOPIC

General Features

- Tends to be polypoid, beefy red to grayish pink with hemorrhage
- Soft, edematous, and fleshy

Size

- Range: 0.8-8 cm; mean: 3.1 cm
 - Tumors in females often larger than in males (mean: 3.3 cm vs. 2.8 cm)
- Size does not correlate with recurrence

MICROSCOPIC

Histologic Features

- Surface epithelium usually intact (respiratory-type or metaplastic squamous mucosa)
- Subepithelial proliferation separated from surface (grenz zone)
- Proliferation effaces normal architecture, although entrapped minor mucoserous glands can be seen
- Bone remodeling or compression may occur, but not direct invasion
- Cellular, diffuse, syncytial arrangement
- Many patterns of growth, often within same tumor
 - May be fascicular (short, not long fascicles), storiform, solid, whorled, meningothelial, reticulated, palisaded, peritheliomatous
- Spindled, epithelioid, or rounded cells with indistinct cell borders
- Clear to amphophilic to slightly eosinophilic cytoplasm
- Absent to mild pleomorphism
- Oval to spindle nuclei with coarse nuclear chromatin
- Mitotic figures uncommon (< 1/10 high-power fields [HPFs])
- Atypical mitotic figures absent
- Ramifying, branching pattern of thin-walled vessels
 - Staghorn or antler-like vessels
- Peritheliomatous (perivascular) hyalinization is characteristic
- Extravasated erythrocytes
- Mixture of inflammatory cells in background
 - Eosinophils, mast cells, and rarely lymphocytes
- Tumor giant cells can be seen, but are uncommon

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
Vimentin	Positive	Cytoplasmic	100% of tumor cells
β-catenin	Positive	Nuclear & cytoplasmic	Nearly all tumor cells
Actin-sm	Positive	Cytoplasmic	Majority of tumor cells positive
Actin-HHF-35	Positive	Cytoplasmic	Majority of tumor cells positive
Cyclin-D1	Positive	Nuclear	Strong reaction in nearly all tumor cells
Laminin	Positive	Stromal matrix	Adjacent to neoplastic cells
CD34	Positive	Cytoplasmic	< 5% of cases
S100	Positive	Nuclear & cytoplasmic	< 3% of cases
CD68	Positive	Cytoplasmic	< 2% of cases
GFAP	Positive	Cytoplasmic	< 1% of cases
Bcl-2	Positive	Nuclear	< 1% of cases
CD31	Negative		
FVIIIIRAg	Negative		
CD117	Negative		Only reactive in mast cells
Desmin	Negative		
CK-PAN	Negative		
EMA	Negative		

- Other tumors (solitary fibrous tumor, fibrosarcoma, respiratory epithelial adenomatoid hamartoma) and reactive changes (sinonasal polyps) can be seen
- Malignant: Rare cases with profound pleomorphism, increased mitotic activity, and necrosis

ANCILLARY TESTS

Immunohistochemistry

- Shows myoid phenotype (actins positive); β-catenin (nuclear and cytoplasmic) and cyclin D1 (nuclear)
- Lacks vascular markers in neoplastic cells

Genetic Testing

- *CTNNB1* mutations: There are single nucleotide substitutions within exon 3 codons of the *CTNNB1* glycogen serine kinase-3 beta phosphorylation region
 - Constitutionally activate β-catenin, with results in aberrant nuclear accumulation due to nuclear translocation of the membrane protein

DIFFERENTIAL DIAGNOSIS

Solitary Fibrous Tumor

- Spindle cell tumor with thin-walled vascular proliferation and heavy, ropy-keloid-like collagen deposition
- Strong and diffuse CD34, Bcl-2, and CD99 immunoreactivity

Peripheral Nerve Sheath Tumor

- Palisaded growth of spindle cells, including Verocay bodies
- Arranged in Antoni A and B areas, with perivascular hyalinization
- Strong S100 protein and SOX10 immunoreactivity

Leiomyoma

- Fascicles of spindle cells often associated with vessel walls

- Lacks perivascular hyalinization, extravasated erythrocytes, and inflammatory cells
- Positive with actins and desmin, but lacks β-catenin

Lobular Capillary Hemangioma

- Lobular growth around central vessels with ulcerated surface and rich inflammatory infiltrate

Nasopharyngeal Angiofibroma

- Nasopharynx origin with heavy stromal hyalinization around variably sized vessels with possible smooth muscle walls

Fibrosarcoma

- Cellular tumor with short, interlacing fascicles of elongated spindle cells with tapered spindle nuclei
- Lacks vascular background, but has increased mitoses and possible necrosis
- Vimentin (+) only

Meningioma

- Whorled pattern of growth comprised of meningothelial or epithelioid cells, occasionally with intranuclear cytoplasmic inclusions

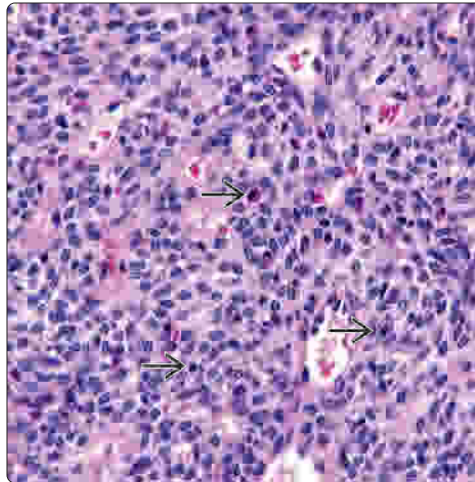
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4. Kuo FY et al: Sinonasal hemangiopericytoma-like tumor with true pericytic myoid differentiation: a clinicopathologic and immunohistochemical study of five cases. *Head Neck*. 27(2):124-9, 2005
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Grenz Zone of Separation

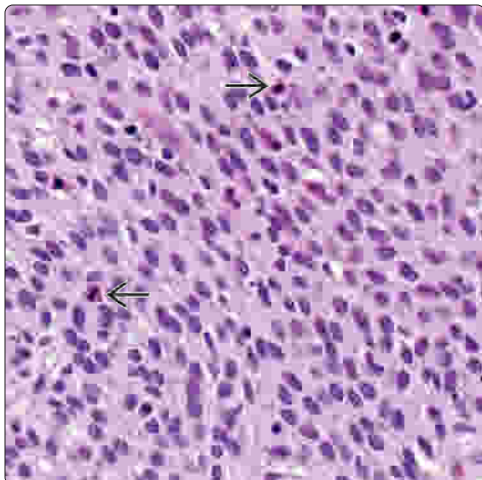


Inflammatory Infiltrate

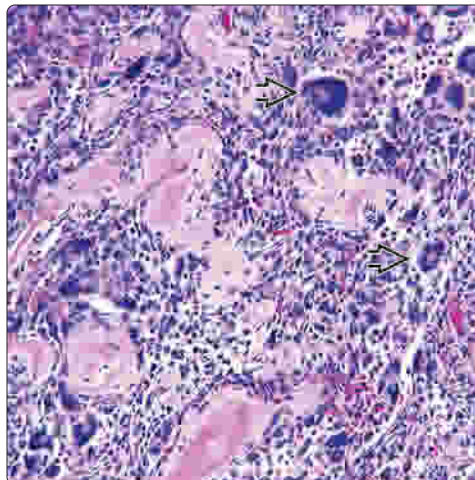


(Left) Hematoxylin and eosin shows an intact, uninvolved respiratory epithelium subtended by a thick band of fibrosis []. Below this is a patternless, bland, cellular proliferation. **(Right)** There is no specific pattern to this proliferation; although, the vessels are easily identified between the lesional cells. Mast cells [], eosinophils, and extravasated erythrocytes are quite characteristic for the tumor.

Eosinophils and Syncytial Pericyte-Like Cells

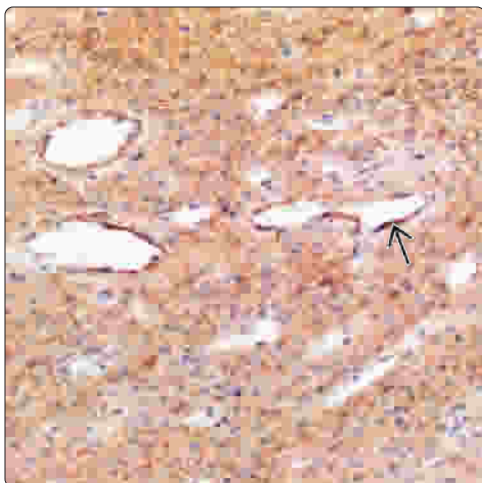


Multinucleated Neoplastic Giant Cells

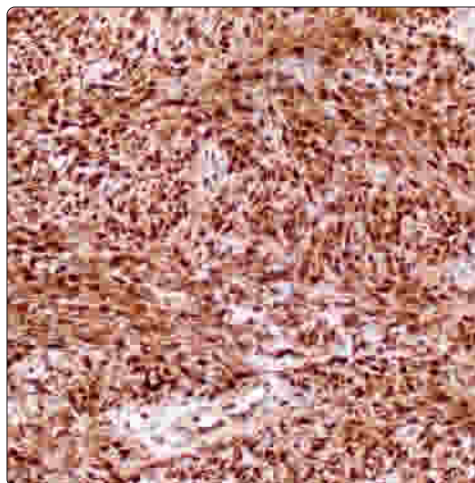


(Left) There is a syncytial arrangement of these ovoid to spindle cells showing no pleomorphism. Eosinophils [] and mast cells are frequently part of the neoplastic milieu. **(Right)** Occasionally, tumor multinucleated giant cells [] will be seen within the proliferation. These cells have an identical immunohistochemistry to the rest of the tumor cells, confirming their neoplastic nature. Note the peritheliomatous hyalinization.

Strong SMA Reaction



β-Catenin Reaction



(Left) The neoplastic cells show a strong and diffuse reaction with smooth muscle actin, a characteristic finding highlighting the myoid phenotype of the tumor (vessels show an internal control []). **(Right)** There is a strong and diffuse nuclear and cytoplasmic reaction with β-catenin, a finding noted as part of the pathogenesis as well as helpful in confirming the diagnosis.

KEY FACTS

TERMINOLOGY

- Malignant epithelial neoplasm arising from surface epithelium with squamous cell differentiation

ETIOLOGY/PATHOGENESIS

- For keratinizing squamous cell carcinoma (SCC)
 - Tobacco smoking
- For nonkeratinizing or partial keratinizing SCC
 - High-risk types of human papillomavirus (HPV)
- May develop from sinonasal (schneiderian) papilloma; majority transform to keratinizing SCC

CLINICAL ISSUES

- Represents ~ 3% of head and neck malignant neoplasms
- Sites in decreasing order of frequency: Maxillary antrum > nasal cavity > ethmoid > sphenoid, frontal
- Treatment includes complete surgical resection plus adjuvant radiotherapy

- Induction chemotherapy may be used in patients with advanced stage disease
- 5-year survival rates include
 - 45% for carcinoma of the maxillary antrum
 - 65% for carcinomas confined to nasal cavity
- Local recurrences frequently occur but metastatic disease is uncommon if the tumor is confined to the involved sinus
- Local failure remains dominant cause of poor outcome

MICROSCOPIC

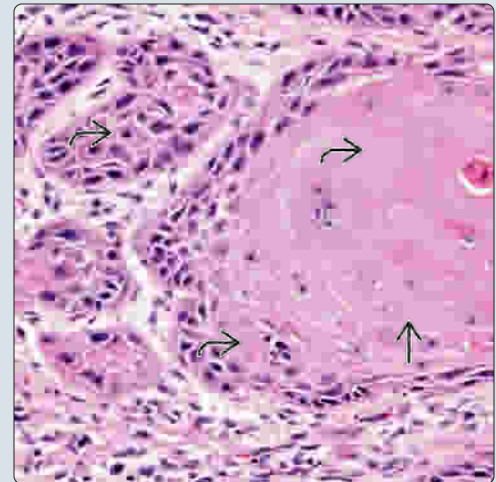
- **Keratinizing SCC**
 - Most common type representing 80-85% of all cases
 - Divided into well-, moderately, and poorly differentiated carcinomas
- **Nonkeratinizing SCC**
 - Represents ~ 15-20% of all cases
 - Often shows downward (inverted or endophytic) growth with broad interconnecting bands or nests of malignant epithelial cells

Sinonasal Keratinizing Squamous Cell Carcinoma

(Left) Sinonasal keratinizing well-differentiated squamous cell carcinoma (SCC) shows invasion into the submucosa characterized by the presence of cohesive nests and cords of carcinoma with an associated desmoplastic stroma. (Right) Readily apparent keratinization and intercellular bridges in association with the invasive (cohesive) tumor nests are characteristic of invasive well-differentiated SCC.

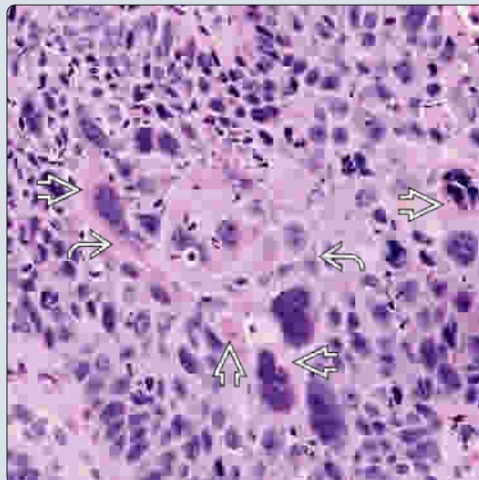


Invasive Well-Differentiated Squamous Cell Carcinoma

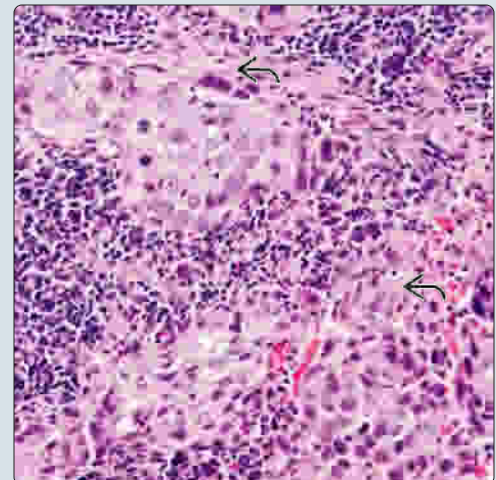


Moderately Differentiated Keratinizing Squamous Cell Carcinoma

(Left) Moderately differentiated keratinizing SCC shows greater nuclear pleomorphism and less differentiation than well-differentiated carcinomas but still retains readily identifiable keratinization and intercellular bridges. (Right) Poorly differentiated SCC retains less identifiable evidence of squamous differentiation, but the nested growth and limited, but identifiable, keratinized cells support this diagnosis.



Poorly Differentiated Keratinizing Squamous Cell Carcinoma



TERMINOLOGY

Abbreviations

- Squamous cell carcinoma (SCC)

Synonyms

- For keratinizing SCC
 - Sinonasal carcinoma
 - Epidermoid carcinoma
- For nonkeratinizing SCC
 - Transitional carcinoma
 - Respiratory epithelial carcinoma
 - Ringertz carcinoma
 - Cylindrical cell carcinoma

Definitions

- Malignant epithelial neoplasm arising from surface epithelium with squamous cell differentiation
 - Histologic subtypes
 - Keratinizing SCC
 - Nonkeratinizing SCC
 - Variants of SCC occur (discussed elsewhere) including
 - Verrucous carcinoma, papillary SCC, spindle cell squamous (sarcomatoid) carcinoma, basaloid SCC, adenosquamous carcinoma, others

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Associated risk factors
 - For keratinizing SCC
 - Tobacco smoking
 - Occupational exposure (textile dust, nickel, prior Thorotrast use)
 - For nonkeratinizing or partial keratinizing SCC
 - High-risk types of human papillomavirus (HPV)

Developmental

- May develop from sinonasal (schneiderian) papilloma
 - Majority transform to keratinizing SCC
 - Majority arise in association with inverted or oncocytic types of schneiderian papilloma
 - Low-risk HPV may be found
 - Direct cause and effect not definitively identified

CLINICAL ISSUES

Epidemiology

- Incidence
 - Represents ~ 3% of head and neck malignant neoplasms
 - Represents < 1% of all malignant neoplasms
 - Most common malignant epithelial neoplasm of sinonasal tract
- Age
 - Most frequent in 6th and 7th decades of life
 - 95% of cases arise in patients older than 40 years
- Sex
 - Male > female

Site

- In decreasing order of frequency, sites of occurrence include

- Antrum of maxillary sinus > nasal cavity > ethmoid sinus > sphenoid and frontal sinuses
- Maxillary sinus
 - No lateralization
- Nasal cavity
 - Primarily lateral wall
 - No lateralization
 - 10% bilateral, although, may represent extension from 1 side via septal perforation
- Nasal septum
 - Rare location for carcinoma with most arising from anterior rather than posterior septum
- Nasal vestibule SCC cutaneous (not mucosal) derived

Presentation

- Maxillary sinus
 - Early symptoms often confused with sinusitis resulting in delay in diagnosis
 - With progression of disease, grouped in 5 categories
 - Nasal: Nasal obstruction, persistent purulent rhinorrhea, nonhealing sore/ulcer, epistaxis, mass
 - Oral: Referred pain, including upper premolar, molar teeth, ulceration, loosening of teeth, fistula
 - Facial: Swelling, asymmetry
 - Ocular: Eyelid swelling, proptosis/exophthalmos
 - Neurologic: Numbness, paraesthesia, pain, cranial neuropathy
- Nasal cavity
 - Unilateral obstruction, nonhealing sore, rhinorrhea, epistaxis
 - Mass
 - Pain in minority of cases

Treatment

- Options, risks, complications
 - Complete surgical resection plus adjuvant radiotherapy
 - Induction chemotherapy may be used in patients with advanced stage disease
 - Favorable response associated with better survival and reasonable chance of organ preservation
- Surgical approaches
 - Surgical advances permit complex tumor removal and reconstruction surrounding these structures
 - Results in functional, cosmetic improvements

Prognosis

- In general, the prognosis is poor
 - 5-year survival rates include
 - 65% for carcinomas confined to nasal cavity
 - 45% for carcinoma of maxillary antrum
- Local recurrences frequently occur but metastatic disease is uncommon if tumor is confined to involved sinus
- Local failure remains dominant cause of poor outcome with death due to disease usually result of uncontrollable local recurrent disease
- Factors portending poorer prognosis include
 - Higher clinical stage disease with involvement of more than 1 anatomic area
 - Extension beyond nasal cavity or paranasal sinuses
 - Results in higher incidence of regional lymph node metastasis

- Regional lymph node metastasis
 - Regional lymph node metastatic rate of ~ 15%
 - Given central location, metastatic disease may occur to ipsilateral or contralateral lymph nodes
 - Primary lymph node drainage is to submental and submandibular lymph nodes; secondary drainage to facial, superficial parotid, and deep cervical lymph nodes
 - Owing to low rate of nodal metastases regional lymph node dissection &/or radiation of regional lymph nodes not advocated as part of initial management protocol
- Pattern of invasion may also impact on prognosis
 - Tumors with diffuse spread or single cell invasive growth pattern have decreased survival of 30-40% as compared to 80-90% survival in patients with more cohesive or pushing pattern of invasion
 - Invasive cancers with single cell or small aggregates of tumor cells invading into host stroma are much more capable of lymphovascular invasion as compared to large cohesive tumor nests
- Presence of HPV associated with better disease-free survival and overall survival than non-HPV cancers
- Nasal vestibule
 - Most patients have excellent prognosis
 - 5-year results include
 - Overall survival of 50%
 - Cancer-specific survival of 74%
 - Locoregional control of 67%
- If present, may vary from mild to moderate to severe dysplasia
- **Grading keratinizing SCC**
 - Divided into well, moderately, and poorly differentiated carcinomas
 - Well- to moderately differentiated carcinomas show
 - Readily apparent keratinization, keratin pearl formation, individual cell keratinization
 - Intercellular bridges
 - Mild to moderate nuclear atypia with enlarged, hyperchromatic nuclei
 - Dyskeratosis (abnormal keratinization)
 - Low mitotic activity
 - Poorly differentiated carcinomas show
 - Less keratinization
 - Greater nuclear atypia
 - Increased mitotic activity, atypical mitoses
 - Evidence of keratinization usually focally present
- **Nonkeratinizing SCC**
 - Represents ~ 15-20% of all cases
 - May have papillary or exophytic growth pattern
 - Often shows downward (inverted or endophytic) growth with broad interconnecting bands or nests of neoplastic epithelium
 - Tumor nests may appear rounded, with smooth borders, or delineated by basement membrane-like material
 - May not be interpreted as invasive but rather as papilloma with severe dysplasia
 - Growth pattern similar to bladder cancers resulting in prior (obsolete) terminology of transitional-type carcinoma
 - Composed of elongated cells with cylindrical or columnar appearance
 - Oriented perpendicular to surface
 - Generally lack evidence of keratinization
 - Keratin may be present focally but does not represent significant component
 - Generally hypercellular neoplasm characterized by
 - Nuclear pleomorphism, hyperchromasia
 - Increased nuclear:cytoplasmic ratio
 - Loss of cell polarity
 - Increased mitotic activity, including atypical forms
 - Dysplasia of surface epithelium may be seen
 - May vary from mild to moderate to severe

IMAGING

Radiographic Findings

- Indispensable in determining extent of disease
- In advanced disease
 - Involved sinus filled by tumor
 - Destruction of bony walls
 - Extension into adjacent structures
 - Oral cavity, skin, infratemporal fossa, periorbital soft tissue, orbit

MACROSCOPIC

General Features

- Polypoid, papillary, fungating, or inverted growth patterns
- May be well circumscribed with expansile growth and limited invasion
- May be overtly invasive with destructive growth, necrotic with friable, hemorrhagic appearance

MICROSCOPIC

Histologic Features

- **Keratinizing SCC**
 - Most common type representing 80-85% of all cases
 - Stromal invasion includes
 - Cohesive nests or cords
 - Isolated invasive malignant cells
 - Desmoplasia present, including collagen deposition ± associated inflammatory cell reaction
 - Dysplasia of adjacent or overlying surface epithelium may be seen
- **Nonkeratinizing SCC**
 - p16(+) (diffuse nuclear and cytoplasmic)
 - Reported in ~ 40% of cases
 - Neuroendocrine markers typically **negative** but patchy staining (e.g., synaptophysin, others) may be present
 - SMARCB1 (INI-1) (+)

ANCILLARY TESTS

Immunohistochemistry

- **Positive** for epithelial markers (e.g., cytokeratins), p63, and p40
- Nonkeratinizing SCC
 - p16(+) (diffuse nuclear and cytoplasmic)
 - Reported in ~ 40% of cases
 - Neuroendocrine markers typically **negative** but patchy staining (e.g., synaptophysin, others) may be present
 - SMARCB1 (INI-1) (+)

DIFFERENTIAL DIAGNOSIS

Schneiderian Papillomas

- Differential diagnosis primarily with inverted-type papilloma
 - Growth characteristics seen in nonkeratinizing carcinoma including broad interconnecting or ramifying cords of tumor is not the pattern seen in association with schneiderian papilloma, inverted type
 - In contrast to carcinomas, schneiderian papillomas
 - Lack malignant cytomorphology
 - Absence of invasive growth lacking
 - Cohesive nests or cords
 - Isolated invasive malignant cells
 - Associated desmoplasia
 - Absence of broad interconnecting cords as evidence in nonkeratinizing SCC

NUT Midline Carcinoma

- Carcinomas originating from midline epithelial structures with balanced chromosomal translocation t(15;19) resulting in *BRD4-NUTM1* oncogene
- Predominantly, but not exclusively, occur in sites above diaphragm, including
 - Head and neck: Most common in sinonasal tract; other head and neck common sites of occurrence include: Nasopharynx, larynx (supraglottic larynx and epiglottis), orbit, parotid gland, and tonsils
- Immunohistochemistry
 - Diffuse reactivity (nuclear staining) for antibodies to NUT protein
 - Cytokeratins (AE1/AE3, CAM5.2, Pank, CK7, CK20) (+); staining may be focal
- Cytogenetics and molecular genetics
 - Translocation involving NUT gene is (15;19)(q13;p13.1)
 - Translocation fuses *NUT1* gene on chromosome 15 to *BRD4* gene
 - In ~ 1/3 of cases, *NUT1* gene fuses to different gene referred to as
- Highly lethal despite intensive therapies

SMARCB1 (INI-1) Deficient Carcinoma

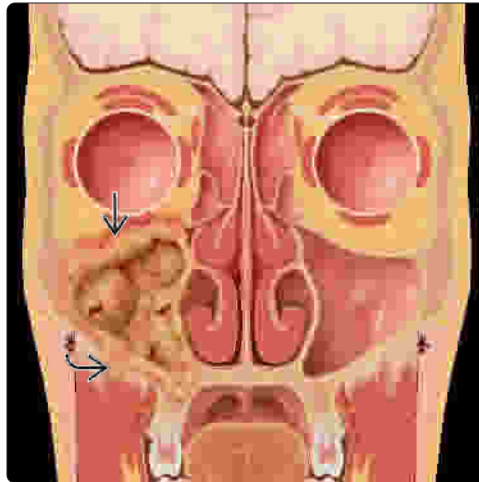
- Primarily comprised of basaloid cells with scattered intermixed rhabdoid cells characterized by abundant, eccentric eosinophilic cytoplasm
- Absence of INI-1 (nuclear) reactivity negative staining in all cases
- Consistent reactivity for cytokeratins (AE1/AE3, CK5) with diffuse or punctate paranuclear staining, latter reported relative to rhabdoid cells

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Schematic Representation

(Left) SCC of the maxillary sinus often presents with extensive invasive growth as depicted in this image by the presence of an invasion of the orbit [X] as well as into the maxilla [X]. (Right) Axial CT demonstrates extensive destruction of the anterior and posterolateral sinus wall [X], with erosion of the posterior maxilla near the pterygoid plates [X].

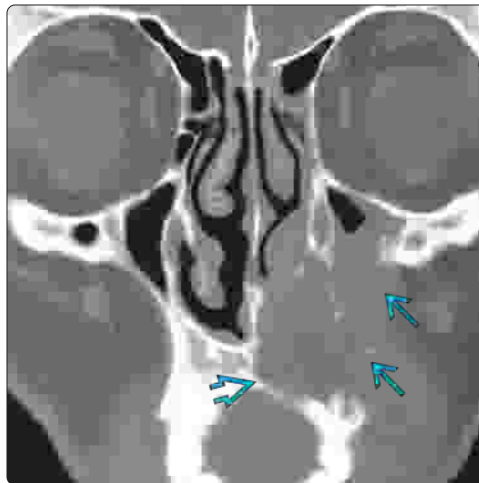


Squamous Cell Carcinoma

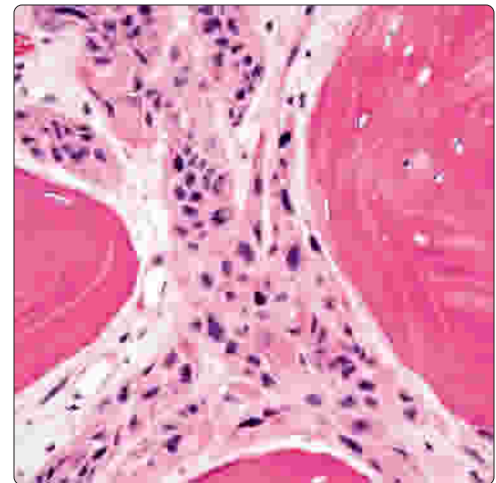


Squamous Cell Carcinoma: Maxillary Antrum

(Left) Coronal bone CT demonstrates aggressive maxillary antral SCC associated with marked bony destruction [X] and extension into the nasal cavity and superior alveolus [X]. (Right) Extensively invasive SCC of the maxillary antrum, including invasion into bone, is shown. The osseous invasion extended within deeper aspects of the cortical bone into the cancellous bone (medullary part), thereby representing a pT4 cancer.

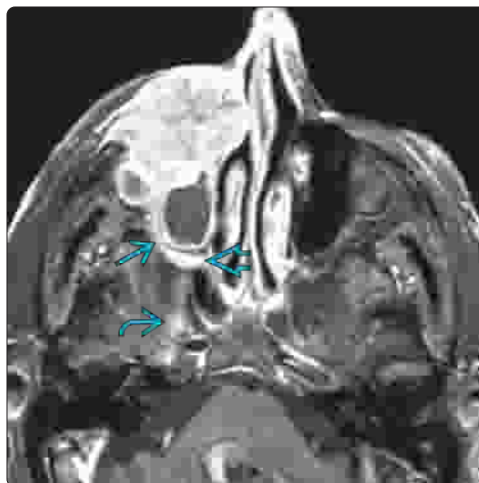


Squamous Cell Carcinoma: Osseous Invasion

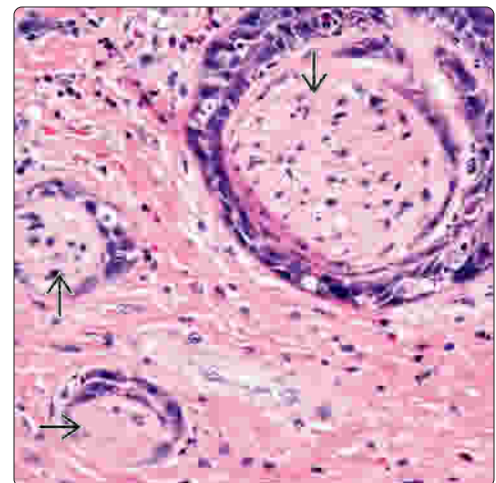


Squamous Cell Carcinoma: Maxillary Sinus

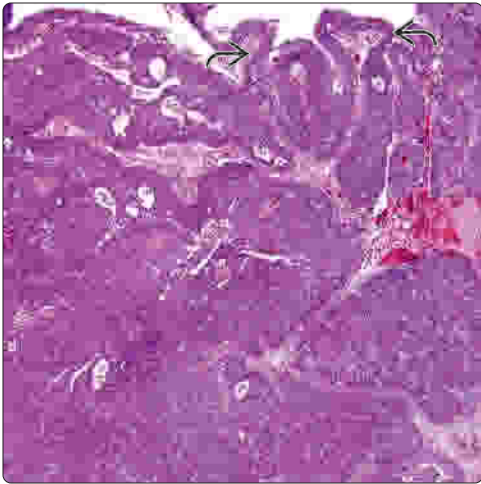
(Left) Axial T1 C+ MR with fat saturation shows an anterior maxillary sinus SCC. V2 perineural tumor [X] enters the pterygopalatine fossa [X]. Note the Vidian canal involvement [X]. (Right) Extensively invasive SCC of the maxillary antrum that includes the presence of a perineural invasion (neurotropism) characterized by cohesive nests of malignant squamous cells wrapping around small peripheral nerves [X] is shown.



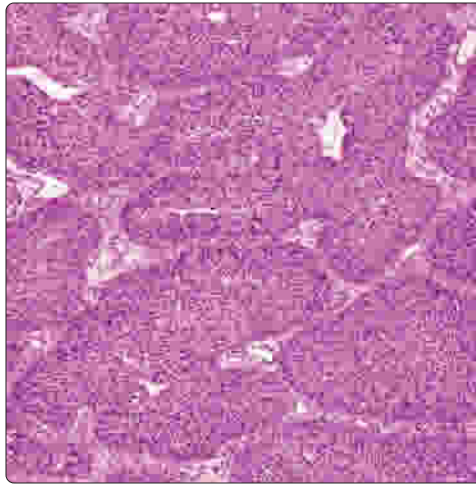
Squamous Cell Carcinoma: Perineural Invasion



Sinonasal Nonkeratinizing Squamous Cell Carcinoma

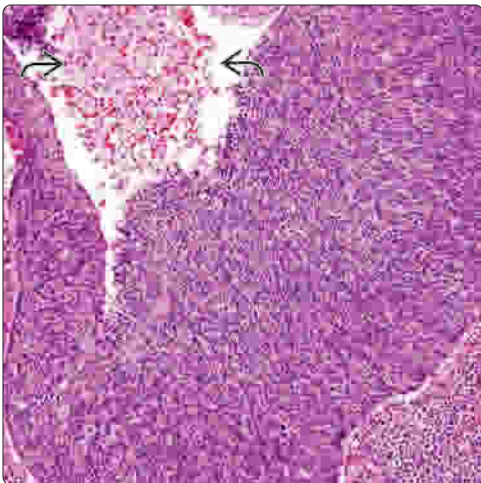


Sinonasal Nonkeratinizing Squamous Cell Carcinoma

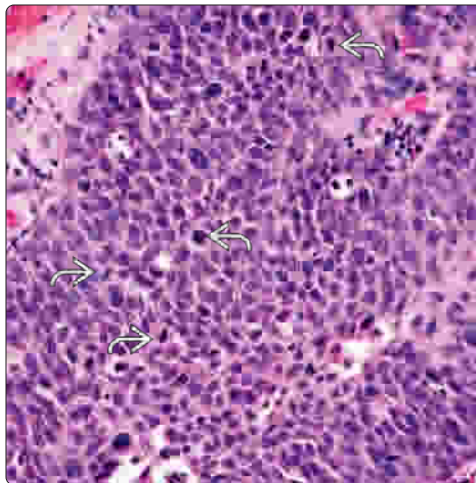


(Left) Nonkeratinizing SCC originates from the surface epithelium and invades into the submucosa as broad interconnecting bands of neoplastic epithelium growing down (inverted) into the stroma. **(Right)** The pattern of growth includes interconnecting/ramifying bands of the neoplastic epithelium, which is a hallmark feature of sinonasal nonkeratinizing carcinoma. This pattern of growth is absent in sinonasal (schneiderian) papillomas.

Sinonasal Nonkeratinizing Squamous Cell Carcinoma

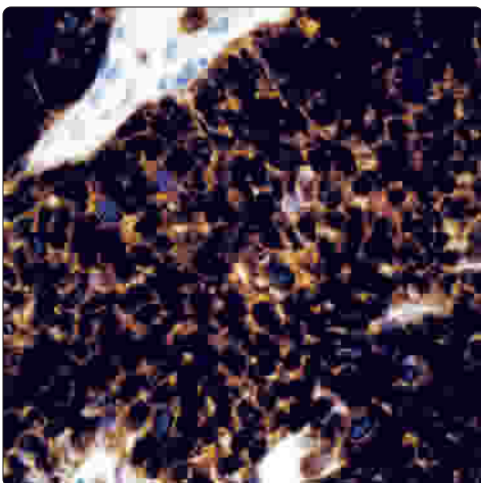


Sinonasal Nonkeratinizing Squamous Cell Carcinoma

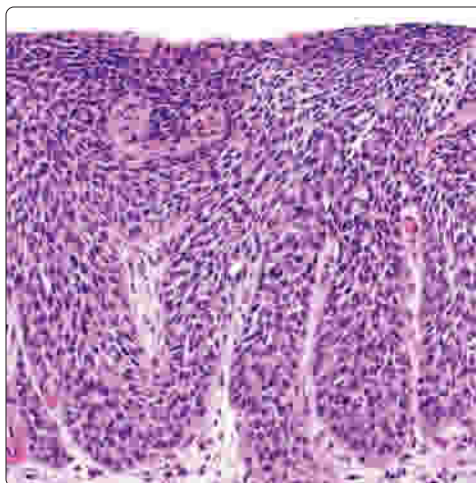


(Left) The neoplastic epithelium is nonkeratinizing and may show cystic change. Such features are similar to nonkeratinizing carcinoma of other head and neck sites. **(Right)** The cytomorphologic features include moderate nuclear pleomorphism, nuclear hyperchromasia, loss of cellular polarity, increased nuclear:cytoplasmic ratio, and increased mitotic activity that may include atypical mitoses. Focal keratinization (not shown) may be present and does not exclude a diagnosis of nonkeratinizing carcinoma.

Sinonasal Nonkeratinizing Squamous Cell Carcinoma



Sinonasal Nonkeratinizing Carcinoma: Carcinoma In Situ



(Left) Diffuse and strong (nuclear and cytoplasmic) p16 immunoreactivity is typically seen in sinonasal nonkeratinizing carcinoma. Molecular analysis (i.e., PCR) confirmed the presence of transcriptionally active HPV, which may confer a better overall prognosis to these cancers. **(Right)** The light microscopic features of SNT (sinonasal tract) NKSCC may include associated surface epithelial CIS, a rather uncommon finding in the SNT in general except in association with invasive SCC or variants.

Sinonasal Undifferentiated Carcinoma

KEY FACTS

TERMINOLOGY

- Highly aggressive and clinicopathologically distinctive carcinoma of uncertain histogenesis
- Composed of pleomorphic cells with frequent necrosis without evidence of squamous &/or glandular differentiation
- Neuroendocrine differentiation by immunohistochemical staining may or may not be present

ETIOLOGY/PATHOGENESIS

- No known etiologic agents
- Not associated with Epstein-Barr virus (EBV)
- Human papillomavirus (HPV) by p16 immunohistochemistry and molecular analysis identified in limited number of cases but relationship to HPV remains uncertain

CLINICAL ISSUES

- Extensively infiltrative at presentation involving multiple sites

- Characteristically, symptoms develop over relatively short duration (weeks to months)

MICROSCOPIC

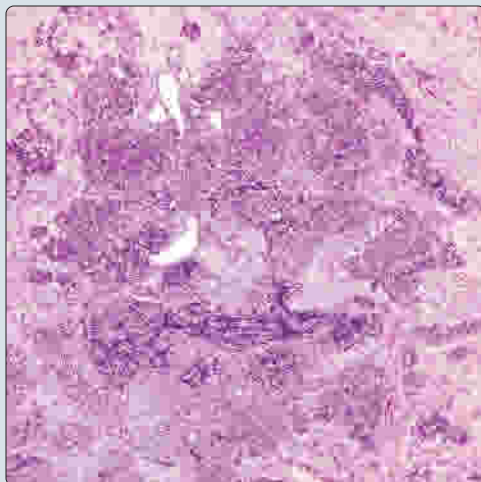
- Hypercellular proliferation with varied growth, including trabecular, sheet-like, ribbon-like, solid, lobular and organoid
- Histologically high-grade undifferentiated neoplastic proliferation with
 - Increased mitotic activity, including atypical mitoses
 - Prominent tumor necrosis (confluent areas and individual cells)
 - Lymph-vascular invasion, neurotropism

ANCILLARY TESTS

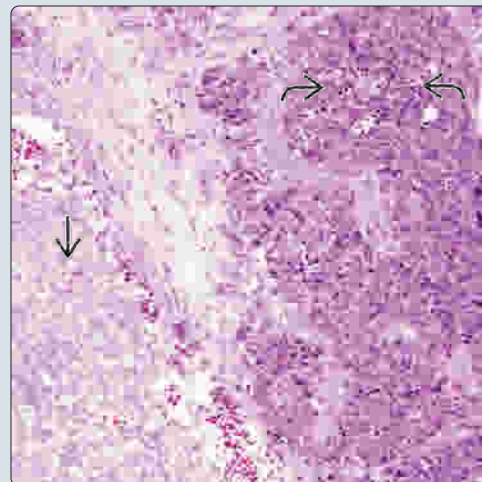
- Consistently immunoreactive with cytokeratins
- Variable reactivity can be identified for p63 with majority showing limited (focal) staining
- Focal reactivity for synaptophysin, chromogranin may be seen; absence of EBER

Invasive Tumor With Lobular Growth

(Left) Invasive neoplasm shows lobular and trabecular growth, a consistent but not pathognomonic feature seen in sinonasal undifferentiated carcinoma (SNUCs). Similar growth characteristics may be seen in other high-grade sinonasal tract (SNT) undifferentiated malignant neoplasms. **(Right)** Undifferentiated malignant neoplasm with associated individual cell necrosis [red box], lies adjacent to a large confluent area of tumor necrosis [blue box], which is a rather common finding in association with SNUCs.

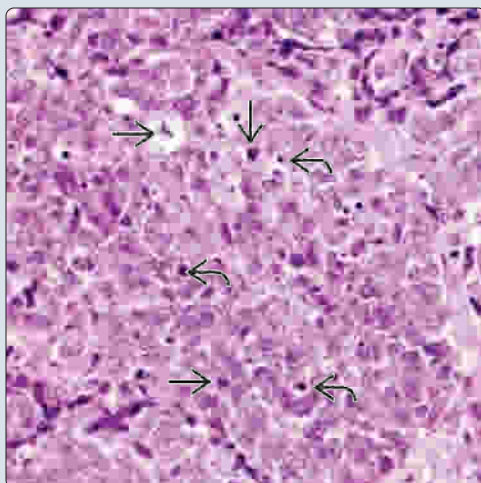


Confluent Necrosis

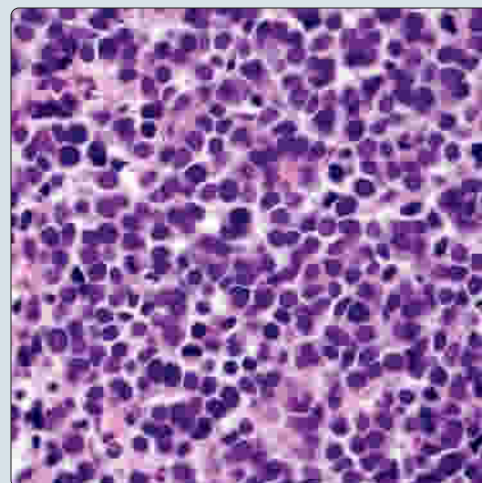


Undifferentiated Malignant Cells

(Left) Histologic similarities to nasopharyngeal carcinoma (NPC), nonkeratinizing undifferentiated type can be seen including cells with enlarged vesicular nuclei and eosinophilic nucleoli. Unlike NPC, SNUCs are negative for EBV and tend to have greater degree of mitotic activity [red box] and necrosis [blue box]. **(Right)** Histologic features of SNUC may also include small cells with round to oval hyperchromatic to stippled-appearing nuclei. Such features may suggest a diagnosis of small cell (neuroendocrine) carcinoma.



Variant Histology With Smaller Cells



TERMINOLOGY

Abbreviations

- Sinonasal undifferentiated carcinoma (SNUC)

Definitions

- Highly aggressive and clinicopathologically distinctive carcinoma
 - Uncertain histogenesis
 - Typically of rapid onset presenting with locally extensive disease
 - Composed of pleomorphic cells with frequent necrosis without evidence of squamous &/or glandular differentiation
 - Neuroendocrine differentiation by immunohistochemical staining may or may not be present

ETIOLOGY/PATHOGENESIS

Idiopathic

- No known etiologic agents
- SNUCs typically negative for Epstein-Barr virus (EBV)
 - Reports of EBV RNA identified in Asian and Italian patients with SNUC but not in other western patients with SNUC
- Human papillomavirus (HPV) by p16 immunohistochemistry and molecular analysis identified in limited number of SNUCs but relationship to HPV remains uncertain
- Some cases reported to develop following radiation therapy for nasopharyngeal carcinoma
- Although no specific etiology linked to development of SNUC, cigarette smoking and nickel exposure identified in patients with SNUC
- Deletion of retinoblastoma gene implicated in development of SNUC

Histogenesis

- Seems reasonable that SNUCs arise from schneiderian epithelium and, therefore, is of ectodermal derivation
- While speculative, given overlapping clinical, light microscopic, immunohistochemical, and ultrastructural features with olfactory neuroblastoma and neuroendocrine carcinoma, cell of origin may be related to both schneiderian membrane and olfactory epithelia
- On basis of finding neuroendocrine features by immunohistochemistry and electron microscopy, it has been suggested that SNUC may be neuroendocrine carcinoma with classification essentially equivalent to pulmonary large cell (neuroendocrine) carcinoma
 - Has not been proven that SNUC represents neuroendocrine neoplasm and is not classified within spectrum of neuroendocrine-type tumors

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon tumor
 - Recognized with greater frequency
- Age
 - Occurs over wide range, including

- 3rd-9th decades of life; median: 6th decade at presentation

- Sex
 - Male > female

Site

- Extensively infiltrative at presentation and involving multiple sites including
 - Nasal cavity
 - One or more paranasal sinuses
 - Orbit, skull base, brain

Presentation

- Multiple symptoms including
 - Nasal obstruction, epistaxis, proptosis, visual disturbances (e.g., diplopia)
 - Facial pain
 - Symptoms of cranial nerve involvement
- Characteristically, clinical symptoms develop over relatively short duration (weeks to months)
 - Rapid onset not typically seen in association with other sinonasal tract (SNT) malignant neoplasms
 - Rapid clinical onset represents helpful, although not pathognomonic, diagnostic finding

Treatment

- Options, risks, complications
 - Multimodality therapy considered best treatment approach to provide best chance for survival and includes radical surgery and postoperative chemoradiation therapy
 - Uncertainty remains in optimal management for SNUC including
 - Sequencing of various therapeutic modalities, optimal chemotherapy agent and dosing, optimal radiation dose and target
 - Significant improvements in outcomes owing to use of multimodality approaches to management
 - For patients who are medically inoperable, definitive chemoradiation therapy used
 - Resectable or potentially resectable tumors receive neoadjuvant chemoradiation therapy followed by surgical resection

Prognosis

- Prognosis for patients treated with definitive radiation therapy ± chemotherapy considered less promising than for those receiving surgery and postoperative radiotherapy ± chemotherapy
- HPV-positive SNUCs may benefit from improved survival but this finding requires further substantiation
- Generally considered highly aggressive neoplasm with poor survival
- Local recurrence common
 - Represents major cause of morbidity and mortality
- Metastatic disease occurs to bone, brain, liver, cervical lymph nodes
- Causes of death primarily related to distant metastases and local invasion

Sinonasal Undifferentiated Carcinoma

IMAGING

Radiographic Findings

- CT and MR often demonstrates large (sinonasal) mass typically with local invasive growth extending beyond its bony confines with involvement of orbital &/or cranial bones
- Intracranial extension may occur

MACROSCOPIC

General Features

- Tend to be fungating with poorly defined margins
 - With invasion into adjacent structures &/or anatomic compartments, including bone destruction

Size

- Typically measure > 4 cm in greatest dimension

MICROSCOPIC

Histologic Features

- Characterized by hypercellular proliferation with varied growth, including
 - Lobular (organoid), trabecular, solid, sheet-like, ribbon-like
- Surface involvement in form of dysplasia/carcinoma in situ usually not present
 - May be present
 - Often ulceration is present precluding evidence of surface epithelial derivation
- Cellular infiltrate consists of
 - Polygonal cells of medium to large size
 - Round to oval, hyperchromatic to vesicular nuclei
 - Inconspicuous to prominent nucleoli
 - Varying amount of eosinophilic appearing cytoplasm with poorly defined cell membranes, although distinct cell borders may be present
 - Cells with clear cytoplasm may be present
- Additional findings include
 - High nuclear:cytoplasmic ratio
 - Increased mitotic activity, including atypical mitoses
 - Prominent tumor necrosis (confluent areas and individual cells), apoptosis
 - Lymph-vascular invasion, neurotropism often present
- 3 cell types described including
 - **Western type** that can be seen to variable extent in single tumor characterized by
 - Cells with round to oval hyperchromatic nuclei, inconspicuous to small nucleoli, limited eosinophilic to amphophilic cytoplasm
 - **Cells similar to nasopharyngeal undifferentiated carcinoma** including large vesicular nuclei, prominent nucleoli, associated (nonneoplastic) lymphocytic infiltrate
 - Reported predominantly in (but not exclusive to) Asian patients
 - **Large cell type** with features similar to large cell carcinoma of lung including large cells with pleomorphic nuclei, prominent eosinophilic nucleoli
 - Reported predominantly in (but not exclusive to) Asian patients

- Neurofibrillary matrix &/or neural rosettes not identified
- Squamous or glandular differentiation should not be present
- Rare examples may show squamous cell differentiation, but in this setting strict criteria required for diagnosis
 - Clinical parameters are those typically associated with SNUC (i.e., rapid onset)
 - Squamous foci (keratinization and intercellular bridges) extremely limited in extent
 - Occurs in neoplasm where dominant histologic features are those of SNUC
 - Presence of an undifferentiated carcinoma with abrupt keratinization may represent *NUT* midline carcinoma and should be evaluated for NUT protein

ANCILLARY TESTS

Immunohistochemistry

- Consistently immunoreactive with epithelial markers, including pankeratins (AE1/AE3, CAM5.2) and simple keratins (i.e., CK7, CK8, and CK19)
 - Reactivity for pankeratins is often intense and diffuse
 - CK4, CK5/CK6, and CK14 reported to be negative
- Variable reactivity can be identified for p63
 - Many cases very limited and focal
 - Some cases are negative
 - Less common is the presence of diffuse positivity
 - p40 may be positive
- INI1 positive (nuclear staining)
- < 50% reported to be positive for epithelial membrane antigen, neuron-specific enolase (NSE) or p53
- S100 protein rarely observed and not in peripheral sustentacular cell pattern characteristically observed in olfactory neuroblastoma
- Focal reactivity for synaptophysin, chromogranin, CD56, CD57 (Leu-7) may be seen
- Vimentin, calretinin, muscle markers (desmin, myoglobin, myf-4, actins) hematolymphoid markers (leukocyte common antigen, B and T cell), melanocytic cell markers (HMB-45, Melan-A, tyrosinase) and CD99 (Ewing marker) are usually absent
- Absence of EBV by immunohistochemical staining (LMP-1) &/or in situ hybridization for Epstein-Barr encoded RNA (EBER)

Genetic Testing

- Sex-determining region Y-Box 2 (SOX2) amplification detected in SNUCs as well as squamous cell carcinoma and carcinomas arising in inverted papillomas suggesting that SNUCs are molecularly closely related to these other cancers
- No other specific molecular profiling identified; SNUCs remain poorly characterized malignancy at both clinical and molecular level

DIFFERENTIAL DIAGNOSIS

Olfactory Neuroblastoma (High Grade)

- Neuron-specific enolase
 - Most consistently positive marker; typically diffuse & strong staining

- S100 protein (characteristic peripheral or sustentacular cell-like pattern)
- Calretinin reactivity typically strong & diffuse
 - SNUCs may be focally calretinin positive
- Neuroendocrine markers (chromogranin, synaptophysin, CD57, CD56) variably positive
- Typically cytokeratin negative
 - Very focal positive staining can be seen
 - Lacks diffuse staining seen in SNUC
 - Rare olfactory carcinoma may show more diffuse cytokeratin staining

Small Cell Undifferentiated Neuroendocrine Carcinoma

- Consistently immunoreactive for neuroendocrine markers (chromogranin, synaptophysin, CD57)
 - SNUCs variably reactive and often nonreactive for neuroendocrine markers

Squamous Cell Carcinoma, Nonkeratinizing

- Tumor grows in broad interconnecting, ramifying cords
- Often p16 positive
- Purported differential cytokeratin staining from SNUC
 - NKSCC: CK5/6, CK13, CK14, p63 positive; CK7 negative
 - SNUC: CK5/6, CK13, CK14 negative; CK7 positive; p63 staining if positive tend to be limited (focal)

Squamous Cell Carcinoma, Keratinizing

- Presence of squamous differentiation (keratinization, intercellular bridges)
- High-grade intraepithelial dysplasia/carcinoma in situ typically present
- Purported differential cytokeratin staining from SNUC
 - SCC: CK5/6, CK13, CK14, p63 and p40 positive
 - SNUC: CK5/6, CK13, CK14 negative; p63 and p40 staining if positive tend to be limited (focal)

Nasopharyngeal Carcinoma, Nonkeratinizing Undifferentiated

- Clinical, radiologic evaluation critical in determining location of tumor
- Presence of EBV
 - SNUCs lack EBV staining

Mucosal Malignant Melanoma

- S100 protein, HMB-45, Melan-A, tyrosinase positive
- Cytokeratin negative

NK-/T-Cell Lymphoma, Nasal Type

- Hematolymphoid markers (CD45, CD3, CD56, others) positive
- Cytokeratin negative (< 5% positive)
- EBER positive
- p63, a marker of epithelial and myoepithelial cells, may be positive

Rhabdomyosarcoma

- Desmin, muscle specific actin, myoglobin, myogenin positive
- Cytokeratin negative (< 5% positive)
- CD56 and CD57 may be positive

NUTMidline Carcinoma

- Poorly differentiated or undifferentiated carcinoma with squamous differentiation
 - Squamous differentiation > 80% of cases
- Diffuse (nuclear) reactivity with antibodies to NUT protein
- Unique chromosomal translocation sole identifier of this disease
 - t(15;19) results in novel fusion oncogene *BRD4-NUTM1*

SMARCB1 (INI1) Deficient Carcinoma

- Rare tumor type characterized by presence of
 - Basaloid cells comprised of enlarged round nuclei with inconspicuous to enlarged nucleoli and scant cytoplasm
 - Rhabdoid cells characterized by abundant, eccentric eosinophilic cytoplasm which may suggest plasmacytoid appearance
- INI1 immunostaining negative
- Loss of SMARCB1 expression characterized by SMARCB1 deletions by fluorescence in situ hybridization

PNET/Ewing Sarcoma


- FLI-1 (nuclear) and CD99 (O13) positive
- Epithelial markers negative to very focally positive
- Defining translocation t(11;22)(q24;q12)



SELECTED REFERENCES

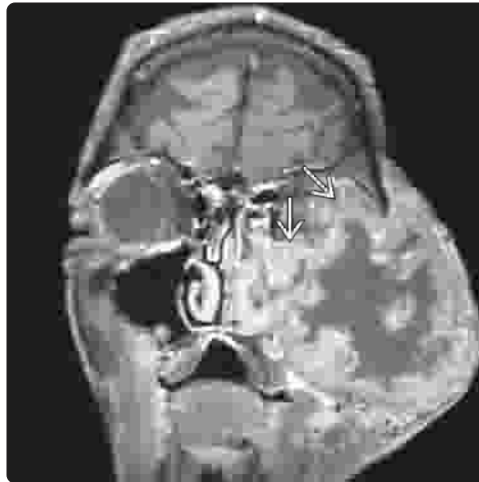
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Sinonasal Undifferentiated Carcinoma

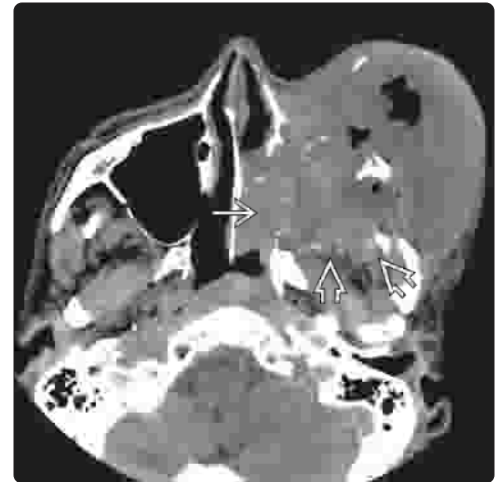
Imaging Findings

(Left) Coronal T1WI C+ FS MR shows a thick, nodular enhancing rim at the periphery of the mass with central necrosis. There is aggressive invasion of the orbit .




(Right) Axial NECT demonstrates a large mass in the left maxillary antrum with marked bone destruction and extension into the nasal cavity , masticator space , and soft tissues of the cheek. Foci of air are seen within the necrotic portion of this rapidly growing lesion.

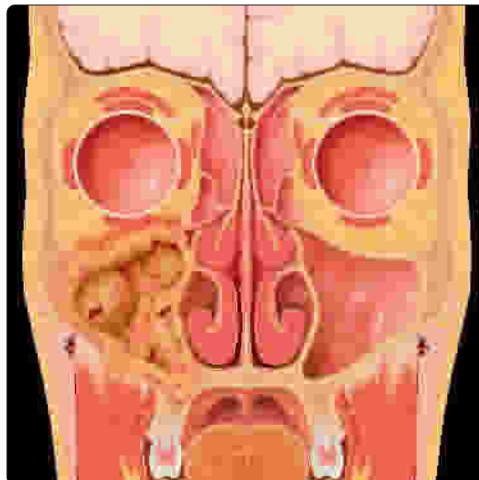


Imaging Findings

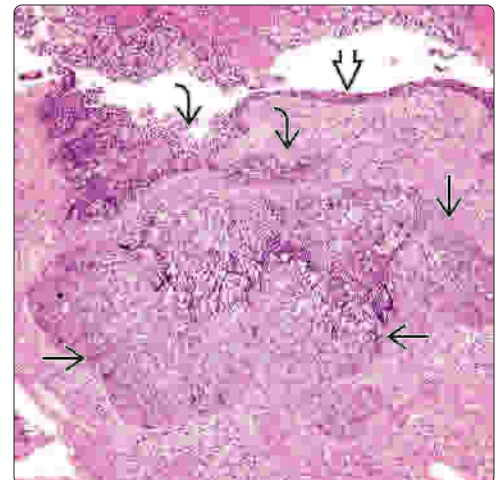


Schematic Representation of Tumor Extent

(Left) SNUCs typically present with extensive local invasive growth as depicted in this image showing a right maxillary sinus carcinoma with destruction and invasion of the floor of the orbit as well as invasion of the maxilla. (Right) Transition from surface epithelium with squamous metaplasia  to carcinoma  is shown. It is uncommon to find intraepithelial neoplasia in SNUCs; such a finding lends support to an origin from the sinonasal epithelium. Submucosal invasive carcinoma with lobular growth is present .

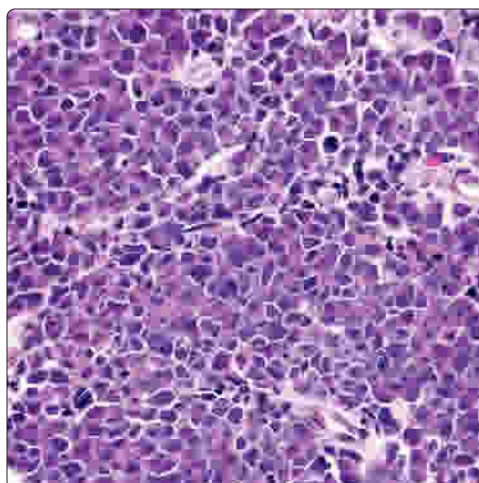


Intraepithelial Neoplasia

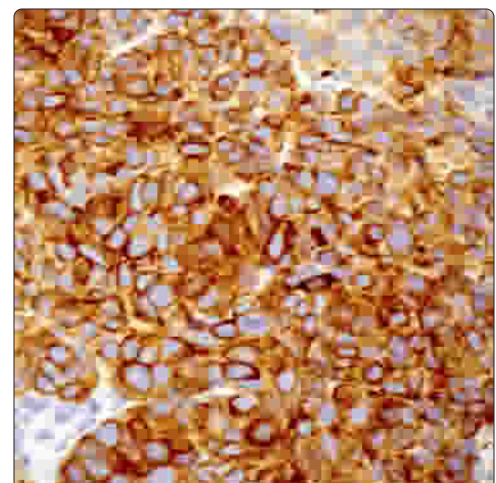


Similarity to Large Cell Neuroendocrine Carcinoma

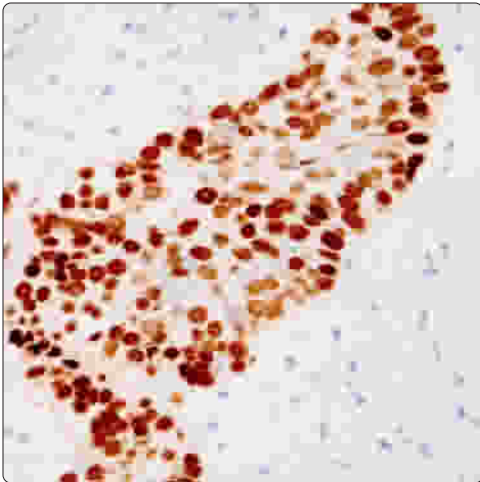
(Left) Undifferentiated malignant cellular proliferation is shown with some similarities to large cell neuroendocrine carcinoma of the lung. The absence of growth patterns more typical of neuroendocrine tumors, absence of neuroendocrine differentiation by IHC staining, and lower mitotic rate (< 10 mitoses per 10 HPF) would exclude a large cell neuroendocrine carcinoma. (Right) IHC antigenic profile of SNUC invariably includes diffuse and strong cytokeratin reactivity.



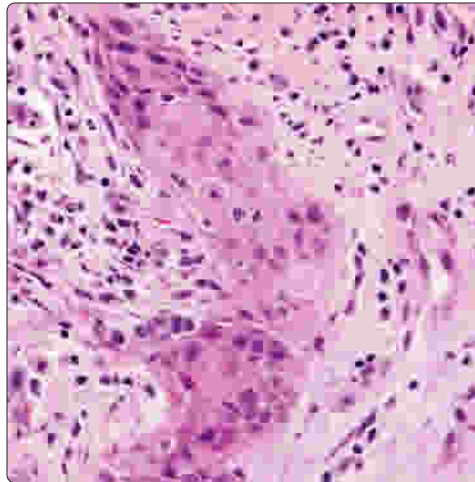
Cytokeratin Staining



p63 Immunoreactivity

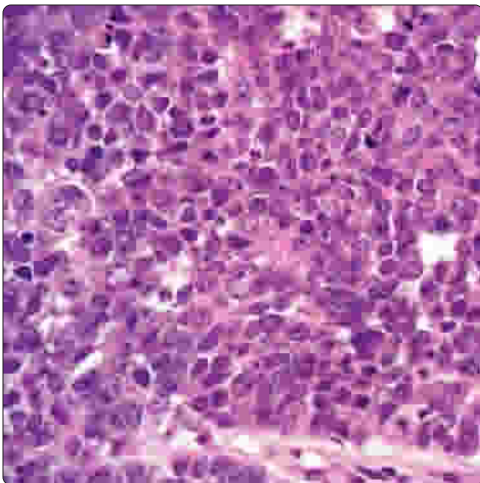


Squamous Cell Differentiation

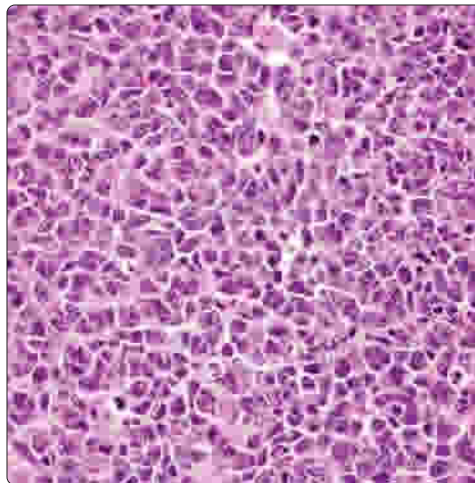


(Left) p63 immunoreactivity, a marker of squamous (and myoepithelial) cell differentiation, varies from case to case and even within the same case. Diffuse (nuclear) p63 reactivity, as illustrated here, is not common as most SNUCs are at best focally p63 positive. **(Right)** Rarely, foci of squamous differentiation may be seen in SNUCs. However, the clinical parameters typical for SNUC must be present. If not, alternative diagnostic considerations include squamous cell carcinoma or NUT midline carcinoma.

Nasopharyngeal Carcinoma

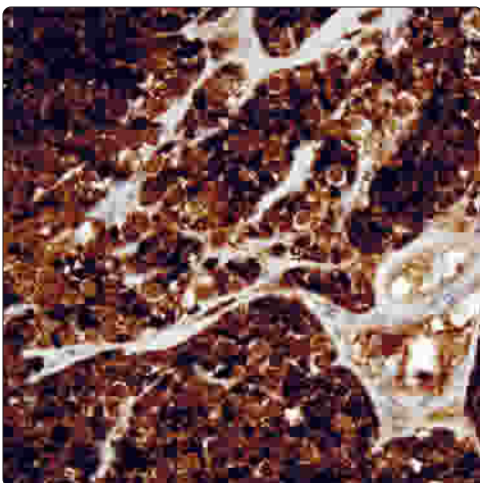


Olfactory Neuroblastoma, High Grade

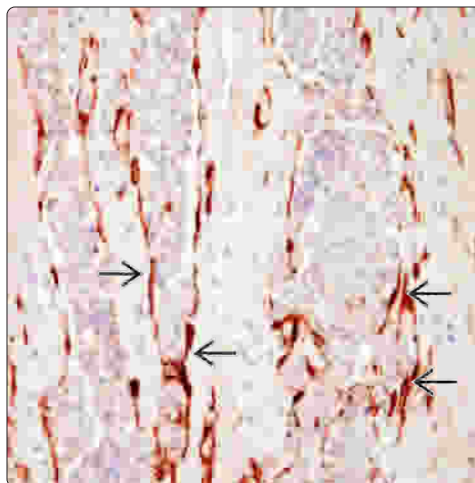



(Left) Nasopharyngeal carcinoma (NPC), nonkeratinizing undifferentiated type may share histologic features and immunohistochemical staining (i.e., cytokeratin) with SNUC. In contrast to SNUCs, the nonkeratinizing undifferentiated type of NPC is almost invariably associated with EBV (not shown). **(Right)** High-grade olfactory neuroblastoma (ONB) may share overlapping histologic features with SNUC, including diffuse or lobular (not shown) growth, increased mitotic activity, and necrosis.

Olfactory Neuroblastoma, Calretinin Staining



Olfactory Neuroblastoma, Sustentacular S100 Staining



(Left) The presence of diffuse and strong calretinin staining is a feature seen in olfactory neuroblastoma of all histologic grades but not typically seen in SNUCs. **(Right)** ONBs show characteristic peripheral S100 protein staining , a finding not usually seen with SNUC or other high-grade SNT malignancies. Immunohistochemical staining generally allows for differentiating high-grade ONB from SNUC.

Lymphoepithelial Carcinoma

KEY FACTS

TERMINOLOGY

- Lymphoepithelial carcinoma (LEC): Rare sinonasal tract carcinoma that is morphologically similar to its better known histologic counterpart in nasopharynx

ETIOLOGY/PATHOGENESIS

- Strong association with EBV
 - Almost all sinonasal LECs associated with EBV

CLINICAL ISSUES

- More common in nasal cavity than paranasal sinuses
- May rarely originate in other upper aerodigestive mucosal sites
 - Parotid gland; larynx; hypopharynx; middle ear
- Radiotherapy represents treatment of choice
- Favorable prognosis owing to good response to radiotherapy

MICROSCOPIC

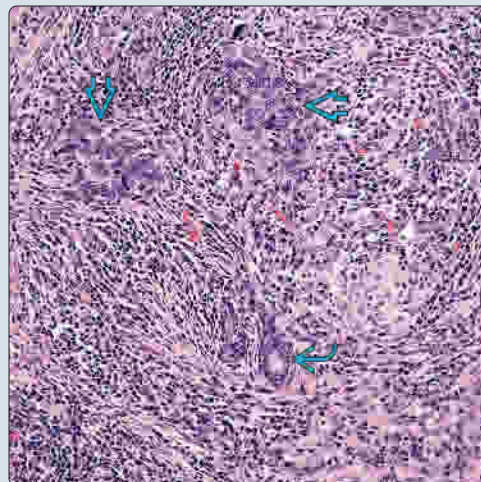
- Submucosal infiltrative neoplastic proliferation characterized by varying growth patterns, including trabeculae, cords, islands, lobules, and sheets often without desmoplastic stromal reaction
- Neoplastic cells include large round to oval nuclei, vesicular appearing chromatin, 1 or more prominent nucleoli, and abundant amphophilic to eosinophilic cytoplasm
- Enlarged round nuclei, prominent eosinophilic nucleoli, dispersed (vesicular) nuclear chromatin
 - Absent keratinization
- In association with carcinoma, dense nonneoplastic lymphoplasmacytic cell infiltrate is commonly present
- Prominent nonneoplastic lymphoid component

ANCILLARY TESTS

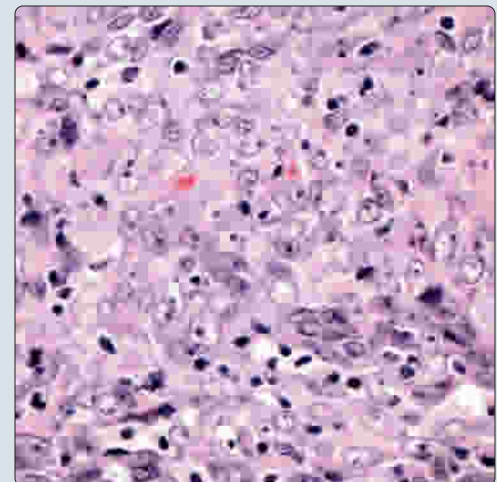
- Cytokeratin (AE1/AE3, CAM5.2), p63(+)
- In situ hybridization for EBV-encoded RNA (EBER) positive

Infiltrative Neoplasm

(Left) Submucosal infiltrative neoplastic proliferation characterized by solid nests with associated prominent lymphoplasmacytic cell infiltrate is shown. Note the absence of associated desmoplastic stromal reaction. Residual minor salivary glands are present. **(Right)** At higher magnification, the lesional cells include large round to oval nuclei with vesicular-appearing chromatin and prominent nucleoli. The presence of indistinct cell borders results in a syncytial appearance.

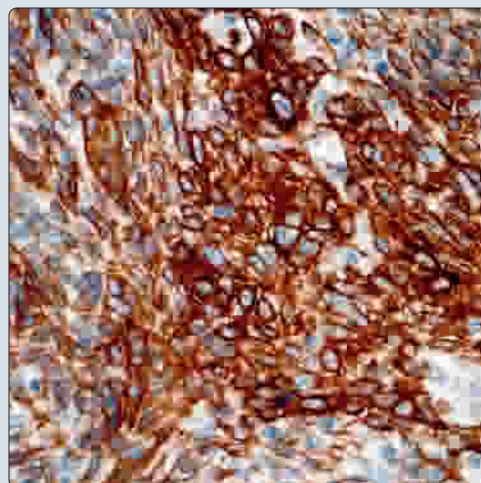


Vesicular Nuclear Chromatin

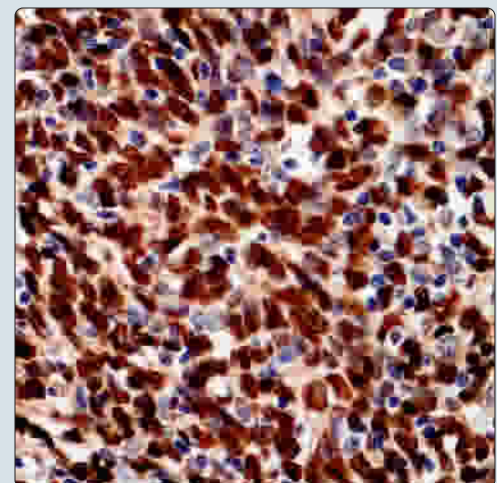


Strong CK-PAN Reaction

(Left) The lesional cells are strongly and diffusely cytokeratin immunoreactive, confirming the epithelial nature of the malignant cells (i.e., carcinoma) and differentiating it from a lymphoma. **(Right)** By in situ hybridization for EBV-encoded RNA (EBER), the lesional cells show strong nuclear staining. In conjunction with cytokeratin staining, the presence of EBER supports a diagnosis of lymphoepithelial carcinoma and allows differentiation from sinonasal undifferentiated carcinoma.



EBER Nuclear Reaction



TERMINOLOGY

Abbreviations

- Lymphoepithelial carcinoma (LEC)

Synonyms

- Lymphoepithelial-like carcinoma; nasopharyngeal-type undifferentiated carcinoma; undifferentiated carcinoma with lymphoid stroma

Definitions

- Rare sinonasal tract carcinoma that is morphologically similar to its better known histologic counterpart in nasopharynx

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Strong association with EBV
 - Almost all sinonasal LECs associated with EBV
 - Only minority of LECs of larynx, hypopharynx are EBV(+)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare
- Age
 - 5th-7th decades
 - Range: 31-75 years
- Sex
 - Male > female (3:1)

Site

- More common in nasal cavity than paranasal sinuses
 - May rarely originate in other upper aerodigestive mucosal sites
 - Parotid gland; larynx; hypopharynx; middle ear

Presentation

- Nasal obstruction, blood-tinged rhinorrhea, epistaxis
- Proptosis, visual disturbances, cranial nerve dysfunction may be present

Treatment

- Radiation
 - Represents treatment of choice

Prognosis

- Favorable owing to good response to radiotherapy
 - 61% disease-free survival reported (median follow-up: 48 months)
- Regional cervical lymph node metastasis may be present at initial presentation
 - Favorable prognosis is not altered even in presence of nodal metastasis

MICROSCOPIC

Histologic Features

- Submucosal infiltrative neoplastic proliferation characterized by varying growth patterns, including trabeculae, cords, islands, lobules, and sheets often without desmoplastic stromal reaction

- May demonstrate syncytial growth with cohesive cells or diffuse noncohesive cellular infiltrate
- Neoplastic cells include large round to oval nuclei, vesicular-appearing chromatin, 1 or more prominent nucleoli, and abundant amphophilic to eosinophilic cytoplasm
 - Indistinct cell borders results in syncytial appearance
 - In association with carcinoma, dense nonneoplastic lymphoplasmacytic cell infiltrate is commonly present
 - Typically less prominent as compared to nasopharyngeal carcinoma
 - When abundant, may obscure neoplastic cells
 - Absent keratinization; intraepithelial dysplasia may be present
- Mitoses and necrosis are uncommon; necrosis may be present, including central comedotype

ANCILLARY TESTS

Immunohistochemistry

- Cytokeratin (AE1/AE3, CAM5.2), p63(+)
- In situ hybridization for EBV-encoded RNA (EBER) positive

DIFFERENTIAL DIAGNOSIS

Sinonasal Undifferentiated Carcinoma (SNUC)

- May share light microscopic & immunohistochemical (i.e., cytokeratins) features with LEC
- Differentiation based on clinical presentation, light microscopy, association with EBV
 - Rapid clinical onset and growth of tumor typical for SNUC, not LEC
 - SNUC characterized by increased mitotic activity, atypical mitoses, necrosis
 - SNUC not associated with EBV

Nasopharyngeal Undifferentiated Carcinoma

- Identical histologic, immunohistochemical features, shared strong EBV association
- Imperative to exclude sinonasal involvement from nasopharyngeal primary tumor
 - Detailed clinical/radiologic evaluation indicated to determine origin of neoplasm

Mucosal Malignant Melanoma

- Presence of S100 protein and melanocytic markers (HMB-45, Melan-A, tyrosinase, MITF1, SOX10)

Non-Hodgkin Lymphoma

- Presence of hematolymphoid markers (CD45RB), lineage (B-, T-cell) specific markers, CD56

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4. Jeng YM et al: Sinonasal undifferentiated carcinoma and nasopharyngeal-type undifferentiated carcinoma: two clinically, biologically, and histopathologically distinct entities. *Am J Surg Pathol.* 26(3):371-6, 2002
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Sinonasal Adenocarcinoma, Intestinal Type

KEY FACTS

TERMINOLOGY

- Malignant epithelial glandular tumors of sinonasal tract that histologically resemble intestinal adenocarcinoma

ETIOLOGY/PATHOGENESIS

- Exposure to hardwood dust, leather, and softwood
 - Increased incidences in woodworkers and workers in shoe and furniture industries
- May occur sporadically without environmental exposure

CLINICAL ISSUES

- May arise anywhere in sinonasal tract (SNT) but in decreasing order of frequency
 - Ethmoid sinus > nasal cavity (inferior and middle turbinates) > maxillary sinus; most sporadically occurring intestinal-type adenocarcinoma (ITACs) involve maxillary antrum
- Complete surgical resection with radiation
- All ITACs considered potentially aggressive, lethal

- 5-year cumulative survival rate is ~ 40%, with most deaths occurring within 3 years
- No difference in behavior between ITACs occurring in occupational exposed individuals and sporadically occurring ITACs

MICROSCOPIC

- Colonic type (40%) prevalence of tubuloglandular architecture, rare papillae
- Papillary type (18%) predominance of papillary architecture with occasional tubular glands
- Solid type (20%) characterized by solid and trabecular growth with isolated tubule formation
- Mucinous type (uncommon) solid clusters of cells, individual glands, signet ring cells, or well-formed glands distended by mucus and extracellular mucin pools

ANCILLARY TESTS

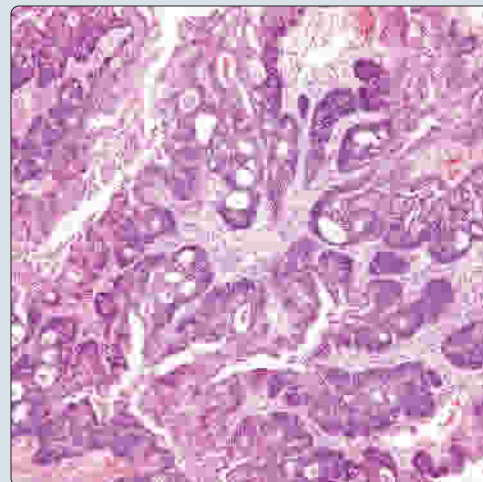
- CK20 positivity (up to 86% of cases) and CDX-2 (nuclear) reactivity

Cystic Areas on CT

(Left) Axial CECT shows a heterogeneous mass with cystic foci, which arises in the anterior ethmoid sinuses, a frequent location for sinonasal adenocarcinomas associated with environmental exposures. The mass shows extensive local invasion, including into the nasal soft tissues. (Right) Colonic-type adenocarcinoma, one of the most common histologic types seen in association with woodworkers and in sporadically occurring cases, is characterized by invasive carcinoma with tubuloglandular architecture.

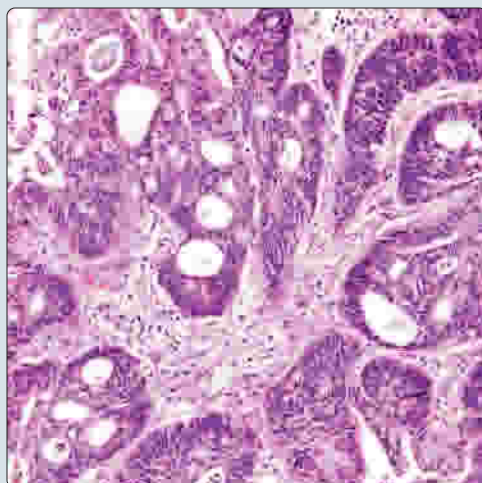


Invasive Adenocarcinoma

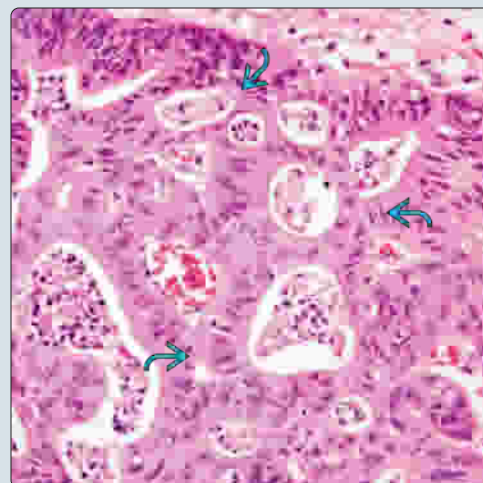


Tubuloglandular Architecture

(Left) The overall features seen here, including tubuloglandular architecture, is virtually identical to primary colonic adenocarcinomas, although this neoplasm originates from within the sinonasal tract. (Right) At higher magnification, the colonic type shows complex glandular growth with back-to-back glands with increased nuclear pleomorphism and mitotic activity. The histologic, histochemical, and immunohistochemical findings are identical to colonic adenocarcinoma.



Complex Back-to-Back Glands



TERMINOLOGY

Abbreviations

- Intestinal-type adenocarcinoma (ITAC)

Synonyms

- Colonic-type adenocarcinoma
- Enteric-type adenocarcinoma

Definitions

- Malignant epithelial glandular tumors of sinonasal tract that histologically resemble intestinal adenocarcinoma

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Exposure to hardwood dust, leather, and softwood
 - Increased incidence in woodworkers and workers in shoe and furniture industries
 - Wood dust exposure shown to be causal factor in mutagenesis of *TP53*, possibly caused by reactive nitrogen species generated through chronic inflammatory process, suggesting role in pathogenesis of ITAC
 - Significant association between COX-2 expression with occupational exposure to wood dust, suggesting role for inflammatory components in carcinogenesis process
- May occur sporadically without environmental exposure

CLINICAL ISSUES

Epidemiology

- Incidence
 - Adenocarcinomas (all types) comprise 10-20% of sinonasal tract malignant neoplasms
 - ITACs are rare
- Age
 - Occurs over wide range
 - Most common in 5th-7th decades of life
- Sex
 - ITAC associated with environmental exposure
 - Male > female
 - ITAC not associated with environmental exposure
 - Female > male

Site

- May arise anywhere in sinonasal tract (SNT) but in decreasing order of frequency
 - Ethmoid sinus > nasal cavity (inferior and middle turbinates) > maxillary sinus
 - Most sporadically occurring ITACS involve maxillary antrum

Presentation

- Early symptoms
 - Nonspecific, varying from nasal stuffiness to obstruction
 - May be associated with epistaxis
- Due to delay in diagnosis, tumors may reach large size with extensive invasion at time of presentation
- Advanced tumors present with pain, cranial nerve deficits, visual disturbances, and exophthalmos

Treatment

- Surgical approaches
 - Complete surgical resection with radiation
 - Depending on extent of neoplasm, surgery varies from local excision to more radical procedures (maxillectomy, ethmoidectomy, and additional exenterations)
 - Neck dissection not indicated
- Radiation
 - Radiotherapy may be utilized for extensive disease &/or for higher grade neoplasms

Prognosis

- All ITACs considered as potentially aggressive, lethal tumors
- 5-year cumulative survival rate is ~ 40%, with most deaths occurring within 3 years
- Generally, are locally aggressive tumors with frequent local failure (~ 50%)
- Metastasis to cervical lymph nodes and spread to distant sites are infrequent, occurring in ~ 10% and 20%, respectively
- Death results from uncontrollable local or regional disease with extension and invasion of vital structures &/or metastatic disease
- Most patients present with advanced local disease, so clinical staging generally has no relevant prognostic significance
- Histologic subtype identified as indicative of clinical behavior
 - Papillary type (grade I) behave more indolently than other histologic variants
- No difference in behavior between ITAC occurring in occupational-exposed individuals and sporadically occurring ITACs

IMAGING

Radiographic Findings

- Essential in determining extent of disease and planning surgery
- Early lesions
 - Soft tissue mass
 - Absent to minimal bone destruction
- More advanced lesions associated with
 - Osteodestruction
 - Invasion of contiguous anatomic structures/compartments
 - e.g., orbit, cranial cavity

MICROSCOPIC

Histologic Features

- 2 histologic classifications proposed
 - Barnes vs. Kleinsasser and Schroeder
 - Either classification is acceptable, but for simplicity Barnes classification is preferred
 - Barnes classification
 - Colonic
 - Papillary
 - Solid
 - Mucinous
 - Mixed

Sinonasal Adenocarcinoma, Intestinal Type

- Kleinsasser and Schroeder classification
 - Papillary tubular cylinder (PTCC) types I-III (I = well differentiated, II = moderately differentiated, III = poorly differentiated)
 - Alveolar goblet type
 - Signet ring type
 - Transitional type
- Barnes papillary, colonic, and solid types correspond to Kleinsasser and Schroeder PTCC-I, PTCC-II, and PTCC-III, respectively
- Most common histologic types seen in association with woodworkers, as well as in sporadically occurring cases that are papillary and colonic types
- **Colonic type**
 - Represents ~ 40% of cases
 - Prevalence of tubuloglandular architecture, rare papillae, with increased nuclear pleomorphism and mitotic activity
- **Papillary type**
 - Represents ~ 18% of cases
 - Shows predominance of papillary architecture with occasional tubular glands, minimal cytologic atypia, rare mitotic figures
- **Solid type**
 - Represents ~ 20% of cases
 - Loss of differentiation characterized by solid and trabecular growth with isolated tubule formation
 - Marked increase in smaller cuboidal cells with nuclear pleomorphism, round vesicular nuclei, prominent nucleoli, and increased mitotic figures
- **Mucinous type**
 - Uncommon type
 - One pattern shows
 - Solid clusters of cells, individual glands, signet ring cells, short papillary fronds ± fibrovascular cores
 - Mucin predominantly intracellular and mucomyxoid matrix may be present
 - Another pattern shows
 - Presence of large, well-formed glands distended by mucus and extracellular mucin pools
 - Pools of extracellular mucin separated by thin connective tissue septa creating alveolar-type pattern
 - Predominantly cuboidal or goblet tumor cells present in single layers at periphery of mucus lakes
 - Mucus extravasation elicits inflammatory response that may include multinucleated giant cells
 - Tumors where mucus component predominates (> 50%) are similar to their gastrointestinal counterparts and may be classified as mucinous adenocarcinomas
- Irrespective of histologic type, ITACs histologically simulate normal intestinal mucosa and may include
 - Villi, Paneth cells, enterochromaffin cells, and muscularis mucosa
- In rare instances, lesion is composed of well-formed villi lined by columnar cells resembling absorptive cells
 - In such cases, bundles of smooth muscle cells resembling muscularis mucosae may also be identified under villi
- **Mixed type**
 - Rare type
 - Composed of admixture of 2 or more of previously defined patterns

ANCILLARY TESTS

Histochemistry

- Mucicarmine: Intracytoplasmic and intraluminal positive
- Diastase-resistant, PAS-positive intracytoplasmic and intraluminal material

Immunohistochemistry

- Strongly reactive with pancytokeratins
- CK20 positivity (up to 86% of cases)
- CDX-2 is nuclear transcription factor involved in intestinal epithelial cell differentiation, and is diffusely expressed in intestinal adenocarcinomas and in sinonasal ITAC
- Expression of villin also present
- Villin and mucin-related antigen MUC2 positive
- Variable CK7 reactivity (43-93% of cases)
- Variably positive for CEA, EMA, B72.3, Ber-EP4, BRST-1, Leu-M1, and human milk fat globule (HMFG-2)
- Absence of myoepithelial-related markers, including p63 and calponin; however, p63 reactivity may be present and does not exclude diagnosis of adenocarcinoma
- Neoplastic cells may express variety of hormone peptides, including serotonin, cholecystokinin, gastrin, somatostatin, and leu-enkephalin
- Chromogranin, synaptophysin, CD56 positivity can be identified
 - Rare examples of mixed ITAC-small cell neuroendocrine carcinoma reported
- p53 immunoreactivity can be identified
- Aberrant expression of p53 and p16 commonly present
 - p53 overexpression less frequent in mucinous subtype
- Increased proliferation rate by Ki-67 (MIB-1) staining

Genetic Testing

- Molecular findings, including
 - *KRAS* mutations in up to 25%
 - *HRAS* mutations variably identified present in some studies and absent in other studies
 - *TP53* mutations from 14-44%
 - Absence of microsatellite instability by PCR
- CGH analyses have shown variety of gains and losses

DIFFERENTIAL DIAGNOSIS

Metastatic Adenocarcinoma of Gastrointestinal Origin

- Rare occurrence to sinonasal tract
- Clinical history critical and mandatory in excluding metastasis to sinonasal tract from primary gastrointestinal tract (GIT) neoplasm
- Histology, histochemistry, and immunohistochemistry of ITAC essentially identical to GIT adenocarcinomas

Sinonasal Nonintestinal-Nonsalivary Adenocarcinoma

- Morphologic features differ from ITACs
- Lack immunoreactivity for gastrointestinal-type markers
 - e.g., CK20, CDX-2, villin, mucins

Salivary Gland Adenocarcinomas

- Most common type in SNT is adenoid cystic carcinoma
- Less common types include

Sinonasal Tract ITACs Classification

Barnes	Kleinsasser and Schroeder	Percentage of Cases	3-Year Cumulative Survival
Papillary type	Papillary tubular cylinder cell I	18%	82%
Colonic type	Papillary tubular cylinder cell II	40%	54%
Solid type	Papillary tubular cylinder cell III	20%	36%
Mucinous type	Alveolar goblet	Uncommon	48%
	Signet ring	Uncommon	0%
Mixed type	Transitional	Rare	71%

- Acinic cell adenocarcinoma
- Mucoepidermoid carcinoma
- Overall histology of salivary gland carcinomas differ from SNT ITACs

Nasopharyngeal Low-Grade Papillary Adenocarcinoma

- Localization to nasopharynx most often along lateral wall
- Immunoreactive for thyroid transcription factor 1 (TTF-1)
- Lack immunoreactivity for gastrointestinal-type markers

Papillary Sinusitis

- Comprised of ciliated respiratory epithelium with simple papillae lacking complex growth
- Absence of dysplastic epithelial changes
- Absence of infiltrative growth
- Lack immunoreactivity for gastrointestinal-type markers

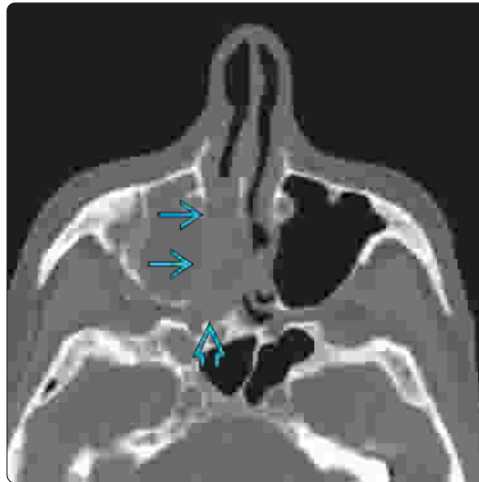
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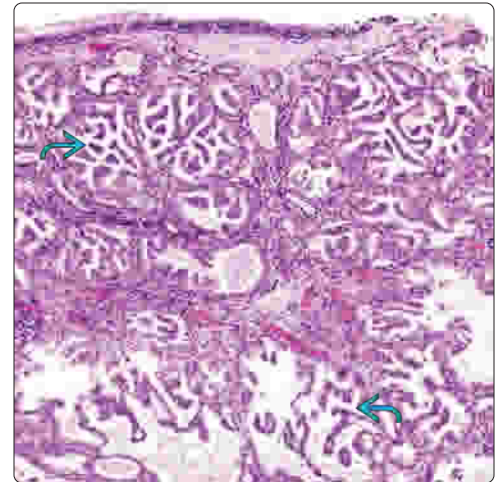
Sinonasal Adenocarcinoma, Intestinal Type

CT Image of Large Tumor

(Left) Axial CT demonstrates a destructive lesion in the right sinonasal tract with erosion of the medial antral wall and spread into the pterygopalatine fossa. (Right) A sinonasal intestinal-type adenocarcinoma (ITAC), of the papillary type, arises in the submucosa and is characterized by the presence of a prominent papillary architecture, as well as glandular growth. These tumors are infiltrative, indicative of a malignant neoplasm.



Prominent Papillary Architecture

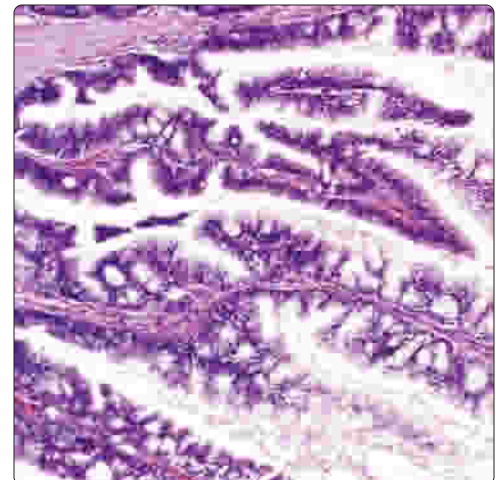


Papillae With Fibrovascular Cores

(Left) The tumor seen here is characterized by the presence of a prominent papillary architecture with fibrovascular cores, although tubular-appearing glands can be seen. (Right) Seen here is papillary architecture with fibrovascular cores and associated glandular differentiation comprised of cells with minimal cytologic atypia and rare mitotic figures (not shown). In spite of the relatively bland cytomorphology, the complex growth and infiltrative growth are diagnostic for adenocarcinoma.

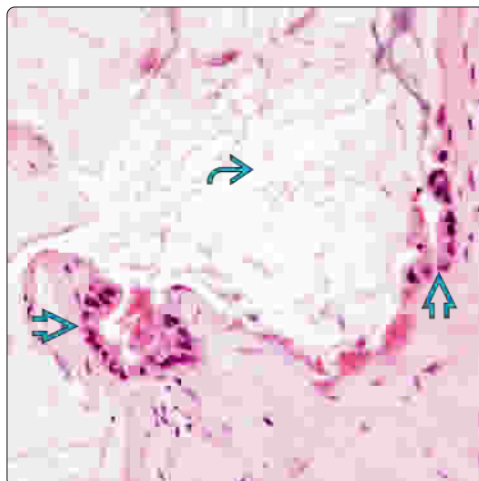


Dysplastic Cells With Minimal Nuclear Atypia

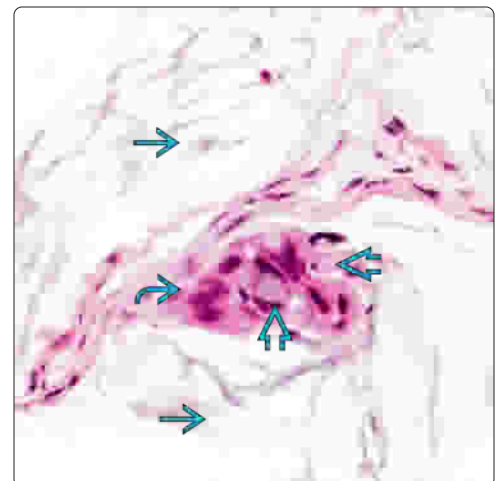


Adenocarcinoma and Mucin Pools

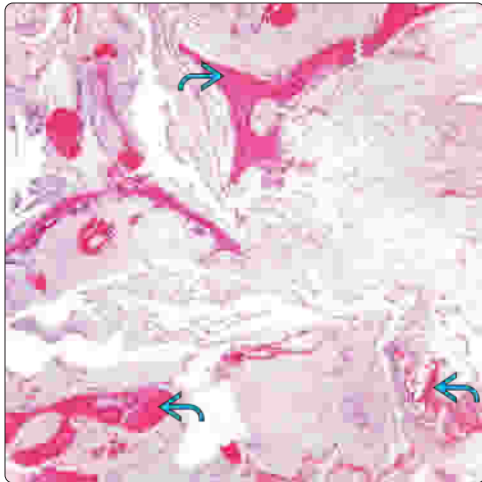
(Left) Sinonasal adenocarcinoma, mucinous type, shows the presence of glands distended by mucus and abundant extracellular mucin pools. (Right) At higher magnification, a gland lined by malignant neoplastic cells, including goblet cells, lies within copious extracellular mucinous pools. The extent of the extracellular mucinous material defines the extent of the tumor, even if epithelial structures are not uniformly seen.



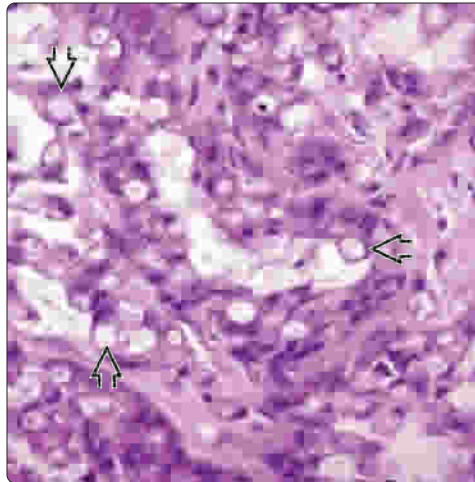
Goblet Cells



Osseous Invasion

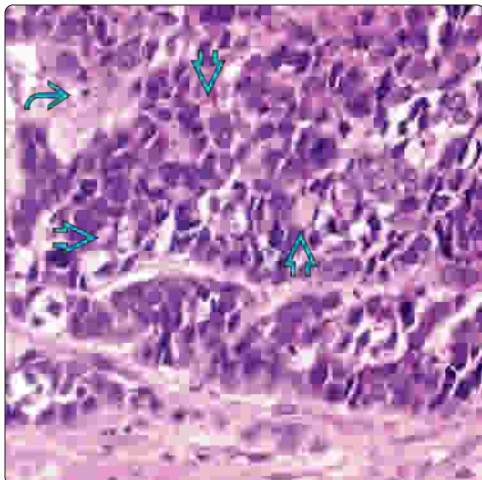


Adenocarcinoma With High-Grade Features

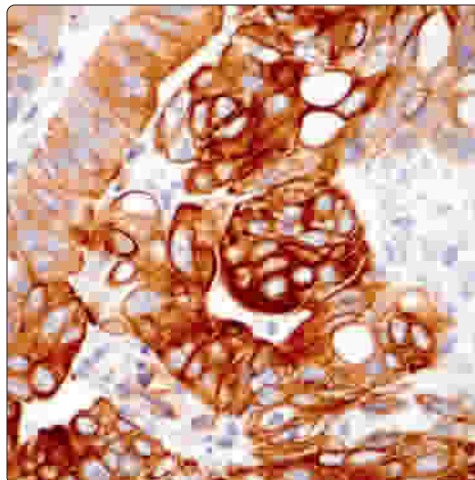


(Left) All types of sinonasal ITACs, irrespective of their histology (including this mucinous type), are capable of aggressive growth with extensive invasion including into bone [2]. (Right) This histologic variant of ITAC includes a solid clusters of cells and individual glands with goblet or signet ring cells [3]; mucin is predominantly intracellular, although mucomyxoid matrix may be present.

Solid Growth With Goblet Cells

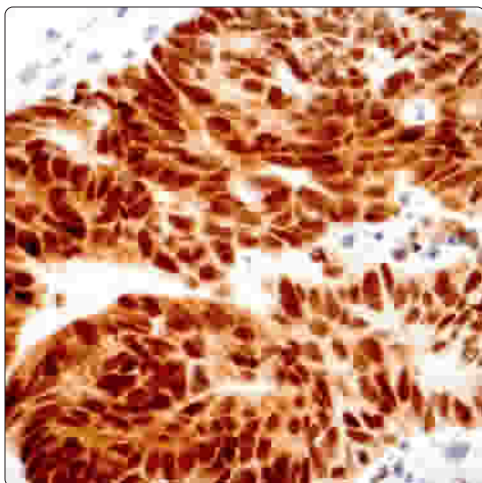


Cytokeratin 20 Expression

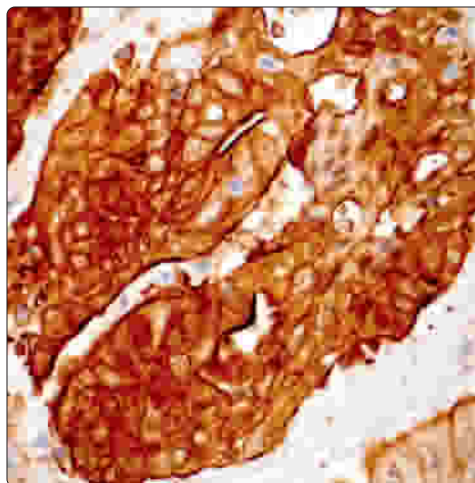


(Left) This solid type of sinonasal intestinal adenocarcinoma shows a loss of differentiation characterized by solid growth with attempts at tubule formation [4], scattered goblet cells [5], and nuclear pleomorphism and increased mitotic figures. (Right) Immunohistochemical staining of sinonasal ITACs is similar to that of primary colonic adenocarcinomas, including the presence of diffuse CK20 immunoreactivity.

CDX-2 Expression



Villin Expression



(Left) In addition to CK20, sinonasal ITACs show diffuse and strong (nuclear) immunoreactivity for CDX-2, a nuclear transcription factor involved in the differentiation of intestinal epithelial cells and diffusely expressed in intestinal adenocarcinomas. (Right) Sinonasal ITACs are also reactive for villin. There is no difference in the histology and immunohistochemical staining between primary colonic adenocarcinoma and ITACs. As such, the clinical history is important in trying to differentiate between ITAC and a metastasis.

Sinonasal Nonintestinal-Nonsalivary Adenocarcinoma

KEY FACTS

TERMINOLOGY

- SNT adenocarcinomas that are not of minor salivary gland neoplasms and do not demonstrate histopathologic features of intestinal types of adenocarcinoma
- Divided into 2 histologic types: Low and high grade

ETIOLOGY/PATHOGENESIS

- No known occupational or environmental factors

CLINICAL ISSUES

- **Low grade**
 - Predilect to nasal cavity and ethmoid sinus
 - Nasal obstruction, epistaxis; pain is an infrequent feature (< 10%)
 - Excellent prognosis: 70-89% 3-year survival rate
- **High grade**
 - Predilect to maxillary sinus
 - Nasal obstruction, epistaxis, pain and facial deformity (e.g., proptosis)

- Dismal prognosis with 20% 3-year survival rate
- Complete surgical excision is treatment of choice for low- and high-grade tumors

MICROSCOPIC

- **Low grade**
 - Submucosal circumscribed gland forming tumor with back to back growth pattern without intervening stroma
 - Glands lined by single layer of nonciliated, cuboidal to columnar cells lacking significant nuclear pleomorphism or mitotic activity
- **High grade**
 - Infiltrative often solid with glandular growth; cells with marked nuclear pleomorphism & increased mitotic activity, including atypical forms

ANCILLARY TESTS

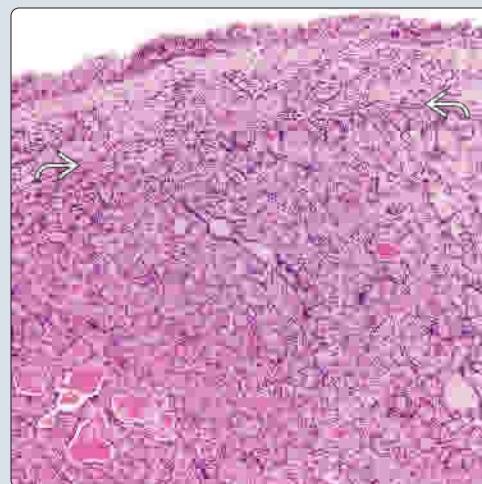
- Reactive for pancytokeratin and CK7; nonreactive for CK20, CDX-2, villin
- p63, calponin, smooth muscle actin usually absent

Sinonasal Adenocarcinoma, Low Grade

(Left) MR shows a nasal cavity adenocarcinoma that has filled the left nasal cavity ➡, obstructed the ipsilateral maxillary sinus, and pushed the nasal septum into the right nasal cavity. This lesion spread along the path of least resistance throughout the nasal cavity but has not yet invaded into the adjacent sinus cavity. (Right) Submucosal, circumscribed but unencapsulated gland forming tumor ➡ shows complex growth characterized by back to back glands with no intervening stroma.

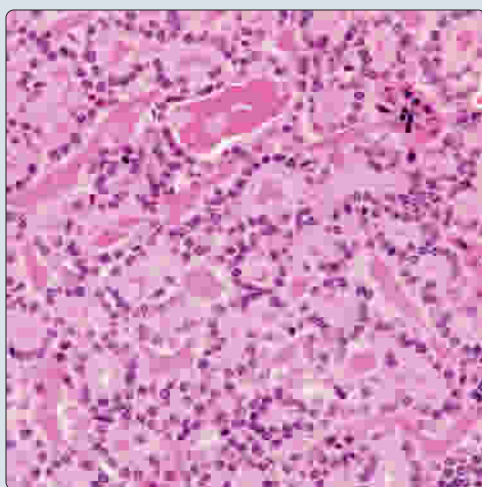


Sinonasal Adenocarcinoma, Low Grade

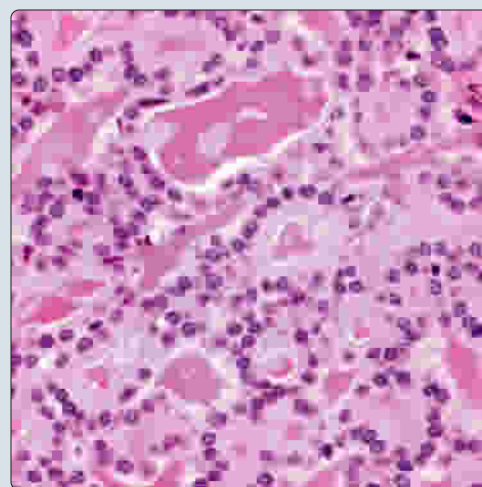


Sinonasal Adenocarcinoma, Low Grade

(Left) Presence of complex growth, including back-to-back glands without intervening stroma & glands lined by a single cell layer, is diagnostic for low-grade adenocarcinoma even with no nuclear pleomorphism, mitotic activity, &/or invasive growth. (Right) At higher magnification, glands are lined by a single layer of nonciliated, cuboidal cells with uniform, round nuclei lacking pleomorphism and mitotic activity. There are no benign neoplasms in the sinonasal tract that have these overall morphologic findings.



Sinonasal Adenocarcinoma, Low Grade



TERMINOLOGY

Definitions

- Sinonasal tract (SNT) adenocarcinomas that are not of minor salivary gland neoplasms and do not demonstrate histopathologic features of intestinal types of adenocarcinoma
 - Divided into 2 histologic types
 - Low grade
 - High grade

ETIOLOGY/PATHOGENESIS

Idiopathic

- No known occupational or environmental factors

CLINICAL ISSUES

Epidemiology

- Incidence
 - Adenocarcinomas (all types) comprise 10-20% of sinonasal tract malignant neoplasms
 - Nonintestinal, nonsalivary gland sinonasal adenocarcinomas are uncommon
- Age
 - **Low grade**
 - Predominantly in adults with mean age at presentation ~ 55-65 years
 - Occurs over wide range (9-89 years)
 - **High grade**
 - Predominantly in adults with mean age at presentation 59 years
 - Occurs over wide range (15-80 years)
- Sex
 - **Low grade**
 - Male > female
 - **High grade**
 - Male >>> female

Site

- **Low grade**
 - May occur at any site but predilect to nasal cavity and ethmoid sinus
 - Ethmoid sinus involvement occurs to lesser extent as compared with intestinal type adenocarcinoma followed by nasal cavity > nasal septum > sinuses (multiple) > maxillary antrum
- **High grade**
 - May occur at any site but predilect to maxillary sinus

Presentation

- **Low grade**
 - Nasal obstruction, epistaxis; pain is infrequent feature (< 10%)
 - Duration of symptoms from 2 months to 5 years with median of 5.5 months
- **High grade**
 - Nasal obstruction, epistaxis, pain and facial deformity (e.g., proptosis)
 - Duration of symptoms from 2 weeks to 5 years with median of 2.5 months

Treatment

- Surgical approaches
 - Complete surgical excision is treatment of choice for low- and high-grade tumors
 - Generally via lateral rhinotomy
 - Depending on extent and histology of neoplasm, surgery varies from local excision to more radical procedures (e.g., maxillectomy, ethmoidectomy, and additional exenterations)
- Adjuvant therapy
 - Radiotherapy may be utilized for extensive disease or for higher grade neoplasms

Prognosis

- **Low grade**
 - Excellent prognosis
 - 3-year survival rate: 70-89%
 - May recur in up to 30% of patients
 - Rarely metastasizes (locoregional, distant)
 - Death due to disease is rare (occurring in < 5% of cases) and is due to uncontrollable local invasion
- **High grade**
 - Dismal prognosis with 20% 3-year survival rate
 - 30% distant metastases

MICROSCOPIC

Histologic Features

- **Low grade**
 - Submucosal unencapsulated glandular &/or papillary growth
 - May be circumscribed
 - Numerous uniform small glands or acini with back-to-back growth pattern without intervening stroma
 - Occasionally, large irregular cystic spaces seen
 - Glands lined by single layer of nonciliated, cuboidal to columnar cells
 - Cells are uniform with round nuclei and eosinophilic to clear- to oncocytic-appearing cytoplasm
 - Nuclei often localized to basal aspect of cell or may demonstrate stratification with loss of nuclear polarity
 - Cellular pleomorphism is mild to moderate
 - Occasional mitotic figures seen, but atypical mitoses and necrosis are absent
 - Invasive growth may be present
- **High grade**
 - Submucosal invasive tumor predominantly with solid or sheet-like growth
 - May show glandular and papillary growth patterns but less as compared to low-grade adenocarcinomas
 - Characterized by presence of
 - Moderate to marked nuclear pleomorphism, increased mitotic activity, including atypical forms, necrosis
 - Invasive growth may include
 - Effacement of normal architecture, angioinvasion, neurotropism, invasion into soft tissues &/or bone

ANCILLARY TESTS

Histochemistry

- Mucicarmine & periodic acid-Schiff with diastase
 - Intraluminal staining; intracytoplasmic staining may be identified
 - Intracytoplasmic staining may be identified

Immunohistochemistry

- Reactive for pancytokeratin, CK7
- Nonreactive for intestinal type markers, including
 - CK20
 - CDX-2
 - Villin
- May be S100 protein positive
- Myoepithelial-related markers, including p63, calponin, smooth muscle actin usually absent
- Typically nonreactive for neuroendocrine markers

DIFFERENTIAL DIAGNOSIS

Intestinal-Type Adenocarcinoma

- Morphologic features differ from nonintestinal, nonsalivary gland-type adenocarcinomas
- Immunoreactivity for gastrointestinal-type markers
 - CK20
 - CDX-2
 - Villin
 - Claudins

Papillary Sinusitis

- In limited biopsy material including only superficial tissue fragments showing papillary epithelial proliferation, differentiation of florid reactive chronic sinusitis with papillary architecture from low-grade adenocarcinoma with papillary architecture can be virtually impossible
- Differentiation is predicated on the presence of back-to-back glands, single cell type and infiltrative growth seen in low-grade adenocarcinomas vs. absence of complex growth pattern, the presence of 2 cell layers and absence of infiltrative growth in papillary sinusitis

Seromucinous Hamartoma

- Submucosal epithelial proliferation of small glands, serous acini and tubules growing in clusters and lobules although haphazard arrangement with larger glands and cysts are seen
 - Typically lack complex growth (back-to-back glands)
- May be surface epithelial derivation with associated foci of respiratory epithelial adenomatoid hamartoma

Sinonasal (Schneiderian) Papilloma

- Surface epithelial derivation
- Histology characterized by
 - Proliferation of epidermoid cells &/or respiratory epithelium including admixture of mucocytes
 - Presence of
 - Intraepithelial cysts
 - Microabscesses
 - Mixed inflammatory cells

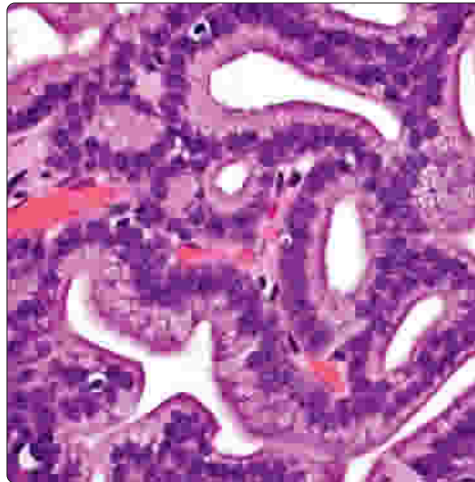
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Sinonasal Adenocarcinoma, Low Grade

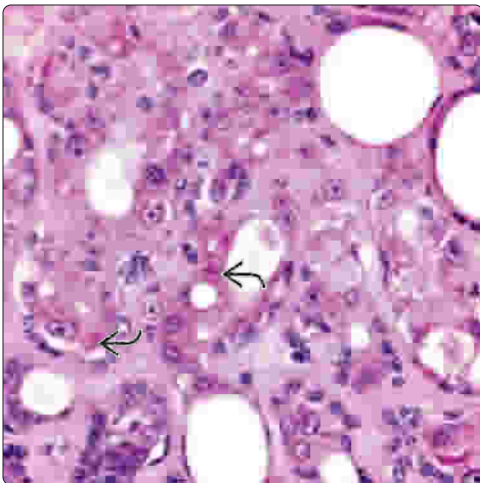


Bland Cytology

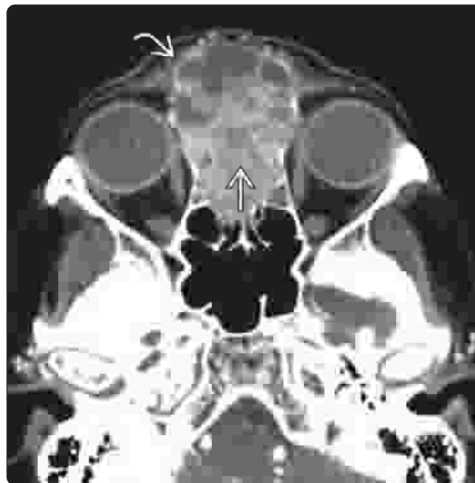


(Left) H&E shows a submucosal, circumscribed but unencapsulated gland-forming tumor with papillary and tubular/glandular architecture and complex glandular growth. (Right) Similar to tumors without papillary architecture, the glands are lined by a single layer of nonciliated, cuboidal cells with uniform, round nuclei lacking pleomorphism and mitotic activity. There are no benign neoplasms in the sinonasal tract that have these overall morphologic findings.

Oncocytic Cells

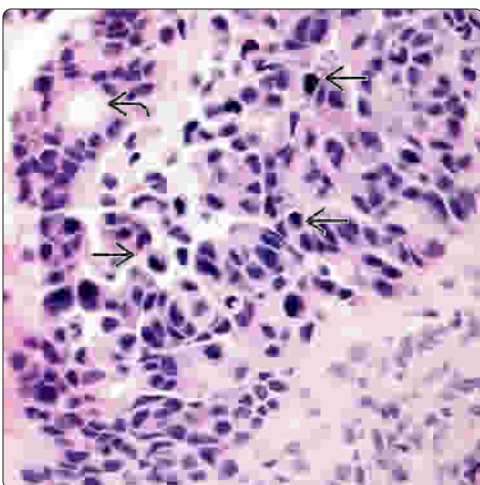


CT of Large Nasal Mass

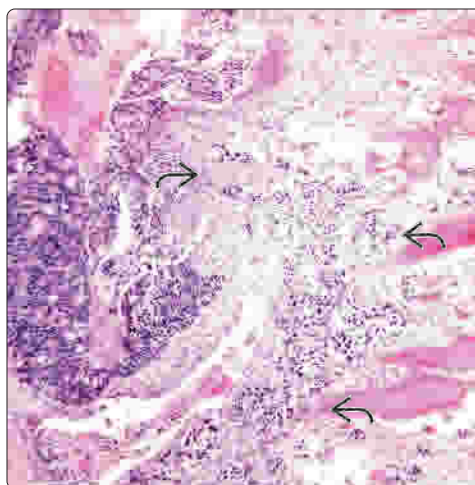


(Left) Sinonasal low-grade adenocarcinoma may also include oncocytic cells characterized by brightly eosinophilic, granular-appearing cytoplasm with enlarged vesicular nuclei and prominent nucleoli. Note the absence of significant nuclear pleomorphism and increased mitotic activity. (Right) Axial CECT shows a heterogeneous mass with cystic foci, which arises in the anterior ethmoid sinuses. The mass shows extensive local invasion including the nasal soft tissues and subcutaneous soft tissues of the forehead.

Sinonasal Adenocarcinoma, High Grade



Bone Destruction



(Left) Sinonasal high-grade adenocarcinoma shows focal glandular differentiation but is predominantly solid with hyperchromatic and pleomorphic nuclei and increased mitotic activity. The light microscopic and immunohistochemical features of this neoplasm contrast to that of intestinal-type adenocarcinomas and salivary gland carcinomas. (Right) Sinonasal high-grade adenocarcinomas are often extensively infiltrative, including invasion into bone as well as into soft tissues and cranial cavity (not shown).

KEY FACTS

TERMINOLOGY

- Malignant neoplasm arising from specialized sensory neuroepithelial (neuroectodermal) olfactory cells

CLINICAL ISSUES

- Bimodal age peak: 2nd and 6th decades
- Unilateral nasal obstruction (70%), epistaxis (50%)
- Nearly always involves cribriform plate of ethmoid sinus
- Consider combination of complete craniofacial resection, radiation, and chemotherapy for best outcome
- Treatment-based 5-year survival: ~85%: Surgery and radiotherapy; 68%: Surgery only; 35%: Radiotherapy only

IMAGING

- Dumbbell-shaped mass with upper portion in intracranial fossa and lower portion in upper nasal cavity

MICROSCOPIC

- Lobular arrangement of primitive neuroblastoma cells around finely fibrillary edematous neural matrix

- **Small round blue cells** (bigger than mature lymphocytes)
 - Small, uniform nuclei with delicate, salt and pepper chromatin distribution
 - Arranged in syncytium, with tangle of neuronal processes
 - **Pseudorosettes** (Homer Wright type) in up to 30% of cases: Neoplastic cells palisaded around finely fibrillary neural matrix
 - **True rosettes** (Flexner-Wintersteiner) in ~ 5% of cases: True tight annular formation by neoplastic cells


ANCILLARY TESTS

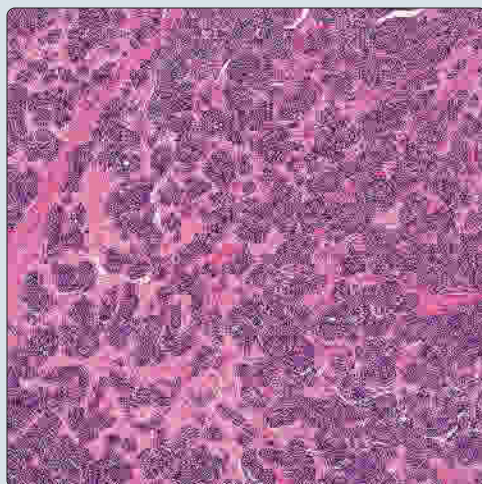
- **Positive:** Neuroendocrine markers; calretinin; S100 protein and GFAP sustentacular cells; rarely, keratin

TOP DIFFERENTIAL DIAGNOSES

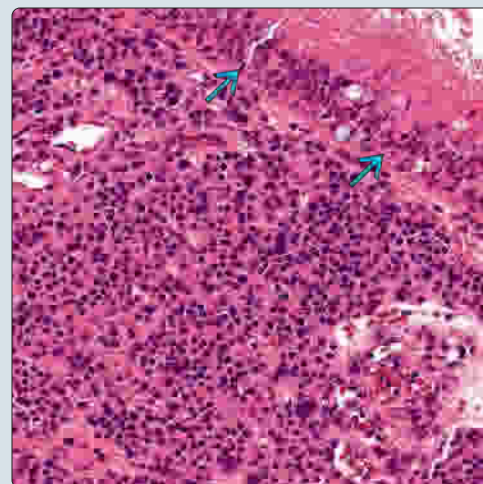
- Sinonasal undifferentiated carcinoma, neuroendocrine carcinoma, extranodal NK-/T-cell lymphoma nasal-type, *NUT* midline carcinoma, rhabdomyosarcoma, PNET/Ewing sarcoma, pituitary adenoma, extramedullary plasmacytoma

Lobular Architecture




(Left) This low-power H&E shows the well-developed lobular architecture of the primitive neuroblastoma cells that is so characteristic for olfactory neuroblastoma (ONB). There are richly vascularized fibrovascular septa. (Right) An intact respiratory epithelial surface  overlies the neoplastic proliferation of small round blue cells. There is a moderate degree of variability in this grade 2 ONB.

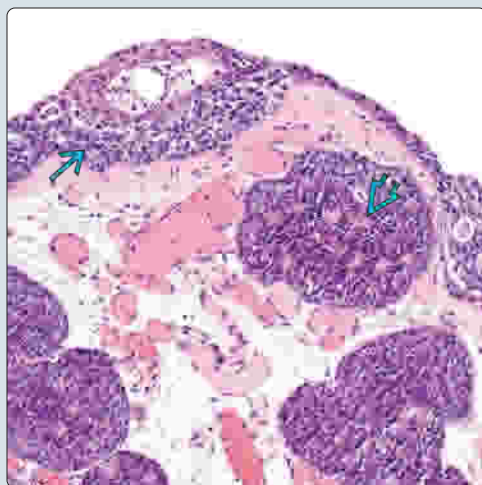


No Surface Involvement

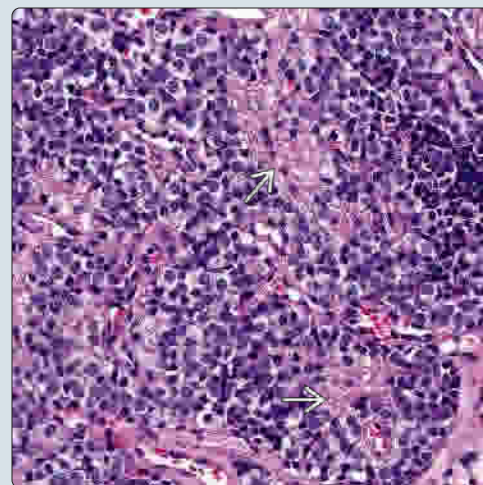


In Situ Olfactory Neuroblastoma

(Left) An intact respiratory epithelial surface  overlies the neoplastic proliferation of small round blue cells. There is an in situ component to the neoplasm. Note numerous rosettes . (Right) There are mildly pleomorphic primitive neuroblastic cells arranged around neural matrix material . These are Homer Wright pseudorosettes, often seen in a grade 1 or 2 tumor.



Neural Matrix in Pseudorosette



TERMINOLOGY

Abbreviations

- Olfactory neuroblastoma (ONB)

Synonyms

- Esthesioneuroblastoma (ENB), olfactory placode tumor, esthesioneurocytoma, esthesioneuroepithelioma, esthesioneuroma

Definitions

- Malignant neoplasm arising from specialized sensory neuroepithelial (neuroectodermal) olfactory cells normally found in upper part of nasal cavity, specifically cribriform plate of ethmoid sinus

ETIOLOGY/PATHOGENESIS

Proposed Origin

- Arise from specialized sensory neuroepithelial olfactory cells (bipolar neurons) of olfactory membrane
- Normally identified in
 - Jacobson organ (vomeronasal organ), sphenopalatine ganglion (pterygoid gland), ectodermal olfactory placode, ganglion of Loci (nervus terminalis), autonomic ganglia of nasal mucosa
 - Olfactory neuroepithelium
 - Cribriform plate; upper 1/3 to 1/2 of nasal septum; superomedial surface of superior turbinate (concha); upper nasopharynx
- Olfactory epithelium contains 3 cell types (also present in tumor)
 - Basal cells (stem cell, thought to give rise to tumor)
 - Olfactory neurosensory cells
 - Supporting sustentacular cells

CLINICAL ISSUES

Epidemiology

- Incidence
 - Represents ~ 2-3% of all sinonasal tract tumors
 - ~ 0.4/1,000,000 population/year
- Age
 - Range: 2-94 years
 - Bimodal peak: 2nd and 6th decades
- Sex
 - Male > female (1.2:1)

Site

- Nearly always involves cribriform plate of ethmoid sinus
- Much less common: Superior nasal concha, upper part of septum, roof of nose

Presentation

- Unilateral nasal obstruction (70%)
- Epistaxis (50%)
- Other symptoms include
 - Headaches, pain, excessive lacrimation, rhinorrhea, visual disturbances
 - Anosmia: < 5% of patients, even though tumor involves olfactory epithelium
- Symptoms are nonspecific, so present for some time
- Rarely, paraneoplastic syndromes may be seen

- Ectopic adrenocorticotrophic hormone (ACTH) or syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Treatment

- Options, risks, complications
 - Due to tumor vascularity, biopsy is discouraged
 - Consider combination of surgery, radiation, and chemotherapy for best outcome
 - Best outcome with combination surgery and radiotherapy (~ 85% 5-year survival)
 - Meningitis, CSF leak (liquorrhea), and dermatitis are potential complications
- Surgical approaches
 - Complete craniofacial resection, including removal of cribriform plate, is treatment of choice
 - Endoscopic-assisted endonasal and anterior craniotomy resection (bi-cranial-facial approach; trephination)
 - Larger tumors tend to be managed by open technique
 - Patients with clear margins do better than those with positive margins
 - Neck dissection recommended if clinically suspicious
- Drugs
 - Chemotherapy is usually reserved for large, high-grade, unresectable, disseminated, &/or salvage
- Radiation
 - Full-course radiotherapy post surgery
 - Patients managed with radiation **alone** have worse outcome
 - Proton-beam therapy may yield better dose distribution
- Autologous bone marrow transplantation: Shows promise

Prognosis

- Overall survival: 70% 5-year survival (stage and grade dependent)
 - Low grade: 80% 5-year survival
 - High grade: 25% 5-year survival
 - Most patients present with Kadish stage C disease
 - Kadish classification is single best predictor of disease-free survival
- Treatment-based 5-year survival
 - ~ 85% for surgery with radiotherapy
 - 68% for surgery only
 - 35% for radiotherapy only
 - 26% for neither surgery nor radiotherapy
- Most tumors show local invasion (orbit, cranial cavity)
- Local recurrence: Up to 30% (range: 15-70%), tends to develop within 1st 2 years after presentation
- 35% of patients develop metastatic disease
 - Cervical lymph nodes (up to 25%): Poor prognosis, < 30% 5-year survival
 - Distant metastases (10%): Parotid glands, lung, bone, liver, skin, and spinal cord
- **Negative** prognostic indicators include
 - High-grade tumor (Hyams grade 3 or 4)
 - Cervical or distant metastasis
 - Kadish Group C
 - Female
 - Age: < 20 or > 65 years at presentation

- Extensive intracranial spread
- Tumor recurrence
- High proliferation index
- Polyploidy/aneuploidy

IMAGING

Radiographic Findings

- Classic appearance: Dumbbell-shaped mass with upper portion in intracranial fossa & lower portion in upper nasal cavity
 - Waist at level of cribriform plate
- Presence of peripheral tumor cysts at intracranial tumor margin is highly suggestive of diagnosis of ONB
- Radiographic findings dependent on tumor size and symptom duration
 - Small: Unilateral nasal mass centered on superior nasal wall
 - Large: Anterior cranial fossa, maxillary sinuses, orbit

MR Findings

- T1WI with gadolinium contrast
 - Avid homogeneous tumor enhancement
 - Enhancement heterogeneous in areas of necrosis

CT Findings

- Bone CT (no contrast)
 - Bone erosion/remodeling of lamina papyracea, cribriform plate, &/or fovea ethmoidalis
 - Speckled calcifications within tumor matrix frequently present

MACROSCOPIC

General Features

- Glistening, unilateral, mucosal-covered, soft, polypoid mass
- Red-gray, with gray-tan to pink cut surface
- Mimics other sinonasal tract primary malignancies

Size

- Range: < 1 cm to huge mass filling nasal cavity and intracranial regions
 - Possible extension into adjacent paranasal sinuses and nasopharynx

MICROSCOPIC

Histologic Features

- Histologic appearance varies based on degree of differentiation
- **Lobular** arrangement of primitive neuroblastoma cells is characteristic (irrespective of grade)
 - Lobule of cells surrounded by richly vascularized stroma creating fibrovascular septa
 - Sustentacular supporting cells line lobule (S100 protein highlighted)
- Surface epithelium is intact, but **in situ** tumor within respiratory epithelium is rarely identified
- Neoplastic cells are classic **small round blue cells**, slightly larger than mature lymphocytes
 - High nuclear to cytoplasmic ratio
 - Small, uniform nuclei with delicate, salt and pepper chromatin distribution

- Nucleoli are small to absent
- Cells arranged in syncytium, with tangle of neuronal processes
 - Centrally located neurofibrillary material creates pseudorosette (Homer Wright type)
- Nuclear pleomorphism, mitoses, and necrosis
 - Absent or limited in low-grade lesions (grade 1 or 2)
 - Present in high-grade lesions (grade 3 or 4)
- 2 types of rosettes are recognized
 - **Pseudorosettes** (Homer Wright type) in up to 30% of cases
 - Neoplastic cells palisading or cuffing around finely fibrillary, delicate edematous neural matrix material
 - Seen in grade 1 and 2 tumors
 - **True rosettes** (of Flexner-Wintersteiner) in ~ 5% of cases
 - Gland-like, tight annular formation by neoplastic cells creating duct-like space with nonciliated columnar cells
 - Seen in grade 3 and 4 tumors
- Peritheliomatous rosettes are not considered of diagnostic utility
- Calcification (psammomatous or concretion) may be seen
 - Decrease in frequency as grade increases
- Rarely present
 - Vascular invasion, ganglion cells or ganglioneuroblastic transformation, melanin-containing cells, rhabdomyoblastic cells
- Tumors are separated into 4 grades
 - Overall grade based on degree of differentiation, presence of neural stroma, mitotic figures, and necrosis

ANCILLARY TESTS

Histochemistry

- Silver stains highlight neurosecretory granules
 - Bodian, Churukian-Schenk, Grimelius

Immunohistochemistry

- **Positive:** Neuroendocrine markers; calretinin; S100 protein and GFAP sustentacular cells
 - Rare reaction with low molecular weight cytokeratin (CAM5.2)
- **Negative:** Desmin, myogenin, CD45RB, CD99

Flow Cytometry

- High rate of polyploidy and aneuploidy, related to adverse prognosis

Genetic Testing

- Chromosomal alterations of 19, 8q, 15q, 22q, 4q
- Deletion of chromosome 11 and gains of 1p associated with increased risk of metastases and worse prognosis
- RT-PCR of human achaete-scute homologue (*hASH1*) expression may be specific marker of ONB
- Sonic hedgehog (Shh) signaling pathway is crucial in tumor development
- **No** *EWS/FLI1* gene fusion

Electron Microscopy

- Membrane-bound dense core **neurosecretory granules** (50-250 µm) present in cytoplasm and nerve processes
- Fibrillary stroma corresponds to immature nerve processes

- Nerve processes may contain neurotubules and neurofilaments
- Flexner-Wintersteiner rosette lining cells may have apical cilia or microvilli and olfactory vesicles

DIFFERENTIAL DIAGNOSIS

Sinonasal Undifferentiated Carcinoma (SNUC)

- High-grade, usually widely destructive neoplasm
- Extensive coagulative necrosis and vascular invasion
- Strong and diffuse keratin immunoreactivity; may show limited neuroendocrine markers

Neuroendocrine Carcinoma

- High-grade tumors with extensive necrosis, high mitotic rate, and apoptosis
- Punctate paranuclear keratin immunoreactivity; may show TTF-1 positive

Extranodal NK-/T-Cell Lymphoma, Nasal Type

- High-grade tumors with extensive vascular invasion and coagulative necrosis
- **Positive:** NK- or T-cell markers; **negative** with neuroendocrine markers, S100 protein, keratin

NUTMidline Carcinoma

- Poorly differentiated, high-grade squamous cell carcinoma, with abrupt keratinization
- Usually in young patients, vast majority in midline, with t(15;19)(q14;p13)

Rhabdomyosarcoma

- Often in same bimodal age distribution; similar radiographic, gross, and clinical findings
- Rhabdomyoblastic differentiation with strap cells and eccentric, eosinophilic cytoplasm
- **Positive:** Muscle markers; keratin and CD56 can be positive in 5-10% of cases

Malignant Melanoma

- Wide variety of architectural patterns and wide variety of morphologic appearances
- Polygonal cells, eosinophilic, plasmacytoid cytoplasm, intranuclear cytoplasmic inclusions and pigment
- **Positive:** S100 protein, HMB-45, Melan-A, SOX10
- **Negative:** Neuroendocrine markers

PNET/Ewing Sarcoma

- Characteristic small round blue cell tumor showing coagulative necrosis
- Diffuse, sheet-like cells with indistinct cell borders, uniform small cells with finely dispersed chromatin distribution and small nucleoli
- **Positive:** FLI-1, CD99, NSE; sometimes synaptophysin; **negative:** Chromogranin, GFAP
- FISH for t(11;22)(q24;q12)

Pituitary Adenoma

- Sphenoid sinus mass, ribbons, festoons, lobular architecture, polygonal cells, lacking pleomorphism and mitoses
- **Positive:** Neuroendocrine and peptide markers, keratin

Extramedullary Plasmacytoma

- Plasmacytoid cells with clock face nuclear chromatin distribution, Hof-zone in cytoplasm
- **Positive:** CD138, CD79a, κ or λ restricted
- **Negative:** Epithelial or neuroendocrine markers

Metastatic Neuroblastoma

- Histologically identical, but has *myc* amplification

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Immunohistochemistry Table

Antibody	Reactivity	Staining Pattern	Comment
Chromogranin-A	Positive	Cytoplasmic	Majority of tumor cells
Synaptophysin	Positive	Cytoplasmic	Majority of tumor cells
CD56	Positive	Cell membrane & cytoplasm	Nearly all neoplastic cells
NFP	Positive	Cytoplasmic	Accentuates neural matrix
S100	Positive	Nuclear & cytoplasmic	Accentuates peripheral sustentacular cells
GFAP	Positive	Cytoplasmic	Highlights peripheral sustentacular cells
Calretinin	Positive	Nuclear & cytoplasmic	> 75% of tumor cells with moderate to strong and diffuse reaction
β-tubulin	Positive	Cytoplasmic	Most tumor cells
CK8/18/CAM5.2	Positive	Cytoplasmic	Only ~ 5% of tumors
Ki-67	Positive	Nuclear	Proliferation index ranges from 5-50%
CD99	Negative		
Myogenin	Negative		
CD45RB	Negative		
p63	Negative		
Bcl-2	Positive	Cytoplasmic	Expression increases with increased tumor grade

Histologic Grading (Hyams Criteria)

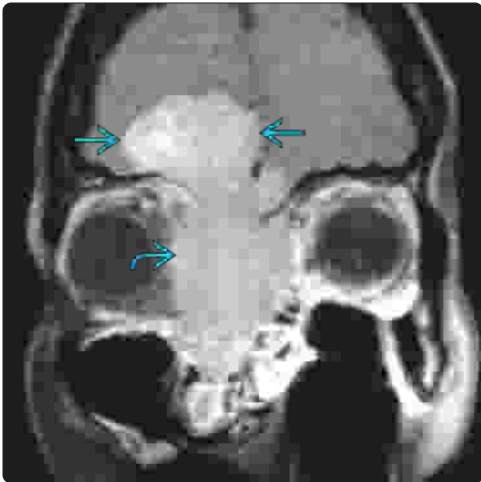
Microscopic Features	Grade 1	Grade 2	Grade 3	Grade 4
Architecture	Lobular	Lobular	± lobular	± lobular
Pleomorphism	Absent to slight	Present	Prominent	Marked
Neurofibrillary matrix	Prominent	Present	May be present	Limited
Rosettes	Homer Wright pseudorosettes	Homer Wright pseudorosettes	Flexner-Wintersteiner rosettes	Flexner-Wintersteiner rosettes
Mitoses	Absent	Present (< 4/10 HPF)	Prominent (4-10/10 HPF)	Marked (> 10/10 HPF)
Necrosis	Absent	Absent	Possibly present	Prominent
Glands	May be present	May be present	Usually limited	Focally present
Calcifications	Variable	Variable	Absent	Absent
Frequency	40-45% of cases	30% of cases	20% of cases	< 10% of cases

Kadish Staging System

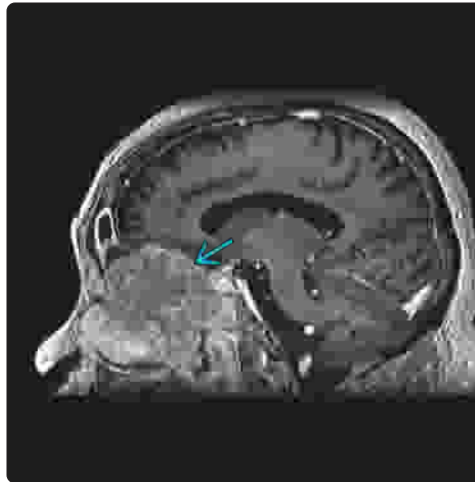
Stage	Criteria	Outcome
Stage A	Tumor confined to nasal cavity (18% of cases)	5-year survival: > 90%
Stage B	Tumor involves nasal cavity plus 1 or more paranasal sinuses (32% of cases)	5-year survival: ~ 70%
Stage C	Extension of tumor beyond sinonasal cavities (50% of cases)	5-year survival: < 50%

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MR of Intracranial Extension of ONB

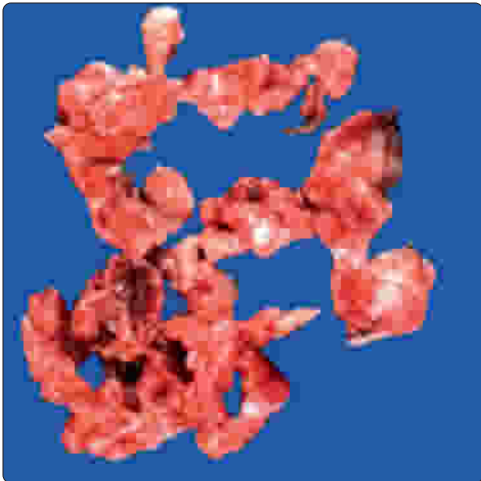


MR of Large Intracranial Extension

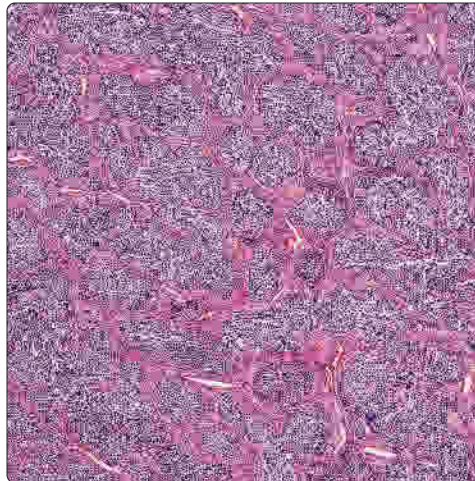


(Left) Coronal T1-weighted contrast-enhanced MR shows slightly heterogeneous enhancement throughout the large mass, destroying the cribriform plate and expanding into the frontal lobe [1]. Extension into the right orbit [2] is also apparent. (Right) Image shows a large mass involving the ethmoid sinus with expansion into the base of the skull and displacement of the frontal lobe [3]. There is a mixed signal, including cysts.

Polypoid Tumor Fragments

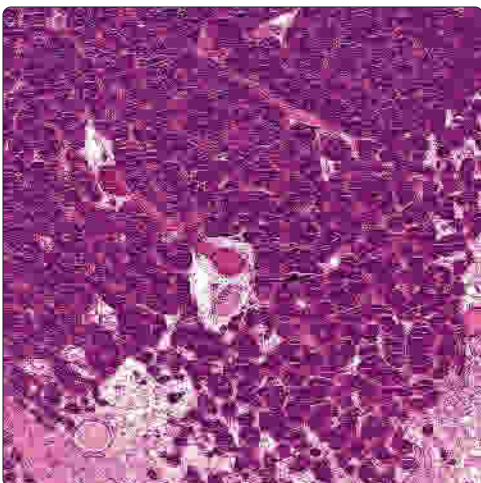


Fibrous Septa and Lobulation

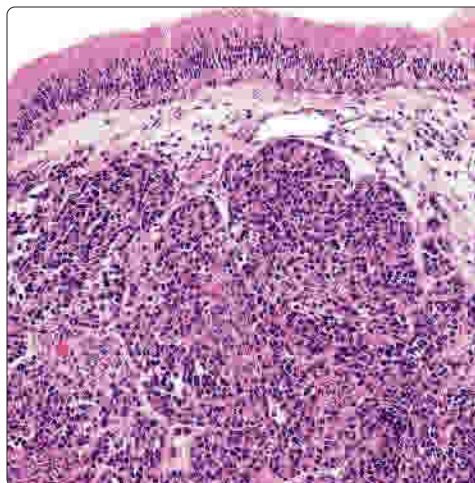


(Left) Multiple polypoid fragments of mucosal-covered soft tissue show a red to red-tan appearance, suggesting rich vascularity of the tumor. (Right) Many fibrovascular septa dissect and surround the tumor lobules, as seen here. The lobular architecture is present to a variable degree in all ONB no matter what the histologic grade is.

Variable-Sized Lobules of Tumor




Subepithelial Lobules of Tumor

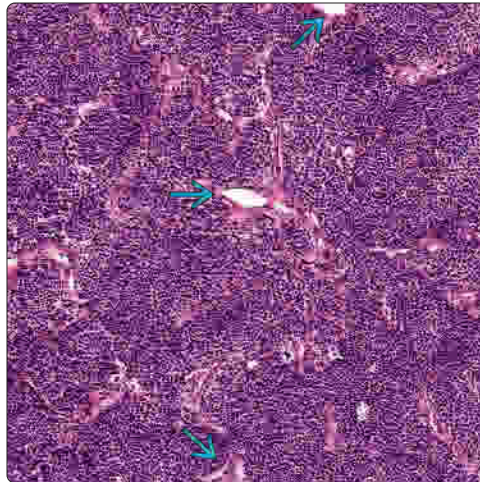


(Left) There are multiple small, tight lobules of tumor set within an edematous to richly vascularized stroma. This lobular architecture is quite characteristic of ONB and is a histologic feature at low power that can be quite helpful in confirming the diagnosis. (Right) The respiratory epithelium seen here is intact, separated by an edematous connective tissue from the lobular neoplastic infiltrate in the stroma. There is limited pleomorphism, with a fibrillary matrix noted between the syncytium of cells.

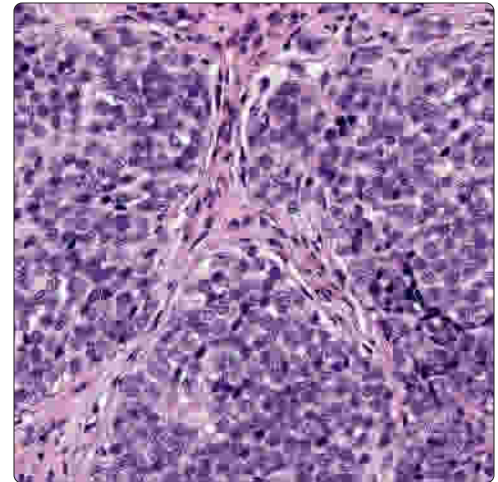
Olfactory Neuroblastoma

Sheets of Neoplastic Cells


(Left) The tumors are quite cellular, showing lobules of primitive neuroblastoma-like cells that have a very high nuclear to cytoplasmic ratio and are arranged in a syncytium. A few vessels  can be easily identified even at this low magnification. **(Right)** This grade 1 tumor shows classic salt and pepper nuclear chromatin without any cellular variability. The fibrovascular septa separate the neoplastic cells into lobules. Neuronal matrix material is noted within the lobules.

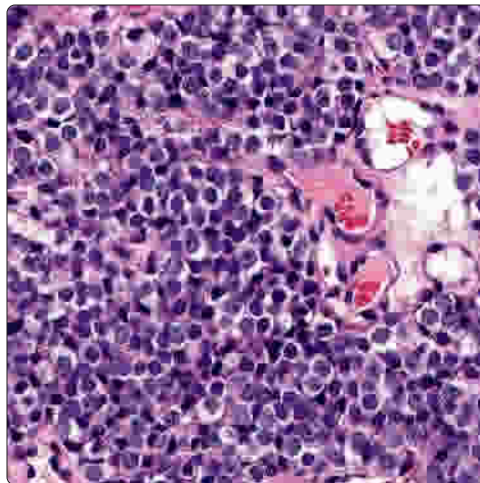


Grade 1 Tumor

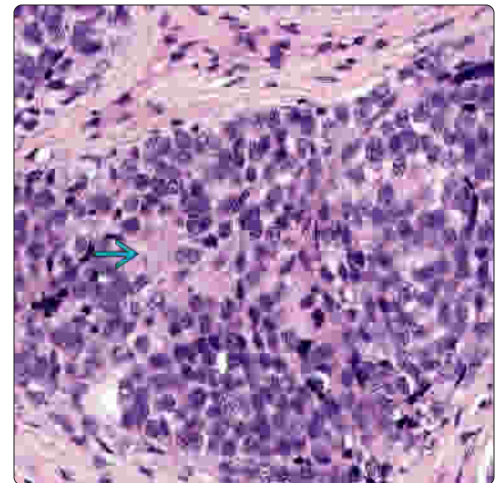


Delicate Nuclear Chromatin


(Left) The neoplastic cells show the small round blue cell pattern so characteristic of neuroblastoma. The nuclei are monotonous, with evenly distributed chromatin. The vascularized stroma is noted. **(Right)** The neoplastic cells are arranged in a syncytium, lacking any well-defined cell borders. There is a high nuclear to cytoplasmic ratio. Nucleoli are focally identified in cells that show delicate salt and pepper nuclear chromatin distribution. Note the Homer Wright rosette , a finding seen in up to 30% of low-grade tumors.

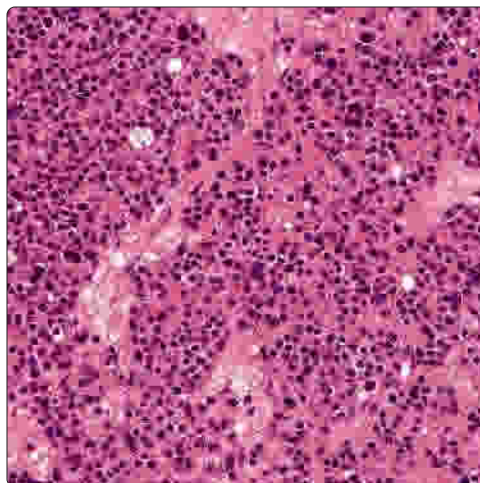


Homer Wright Rosette

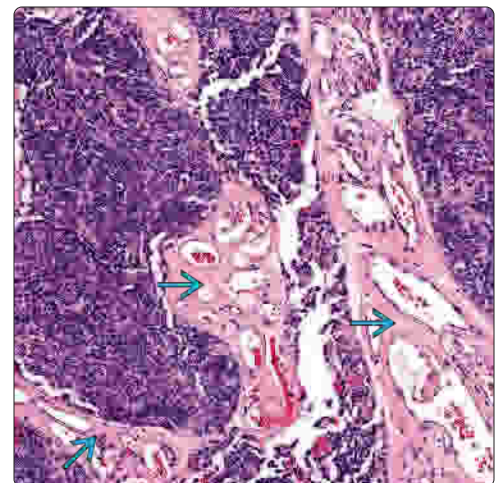


Grade 2 Olfactory Neuroblastoma

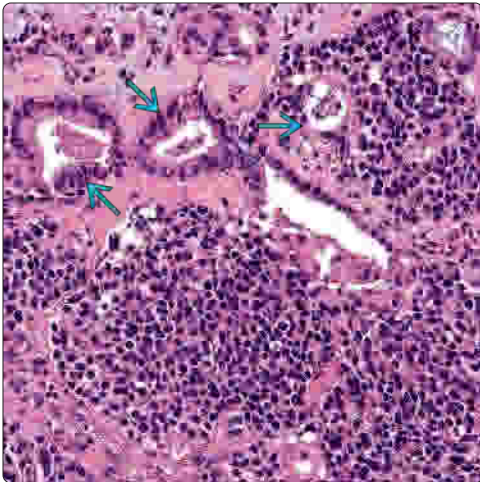
(Left) There is a greater degree of nuclear pleomorphism and variability in this grade 2 tumor, showing nuclear hyperchromasia. Mitoses and necrosis are absent. **(Right)** ONBs are very vascular tumors, with a richly vascularized fibrovascular stroma and septa . This tumor would bleed quite profusely if it were biopsied; hence biopsies are discouraged.



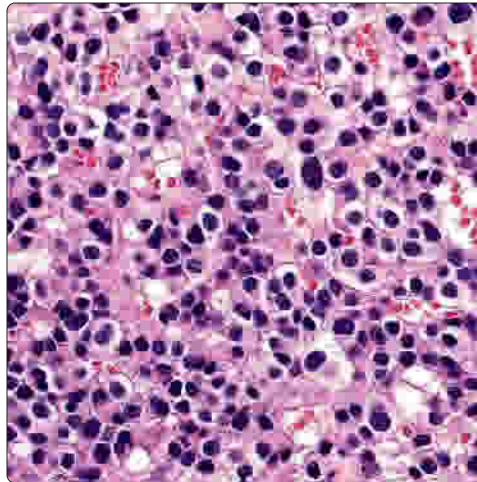
Extensive Vascularized Stroma




Entrapped Minor Mucoserous Glands

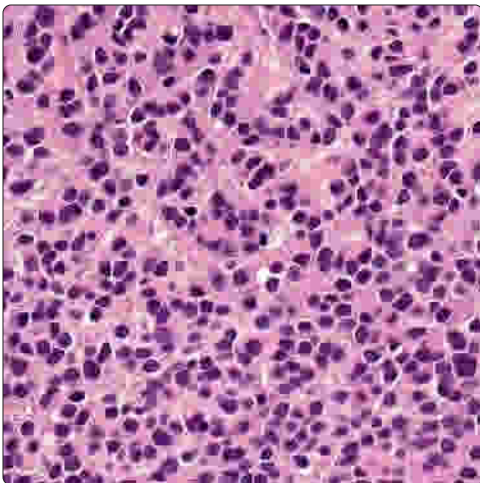


Grade 3 Olfactory Neuroblastoma

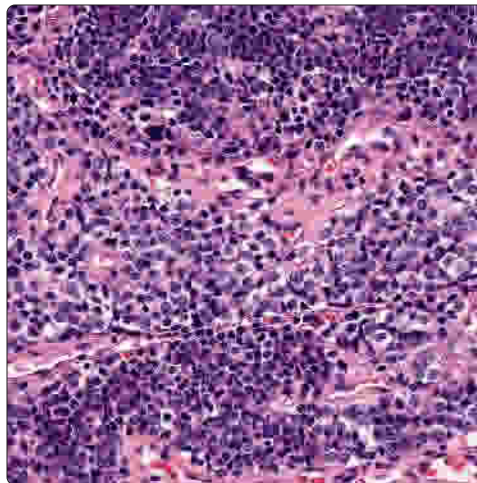


(Left) Native, residual minor mucoserous glands  can be surrounded or invaded by the neoplastic proliferation. It is important to separate these structures from true rosettes (Flexner-Wintersteiner), which are only identified in high-grade tumors. (Right) There is slightly more variability among the nuclei of this tumor, with marked nuclear hyperchromasia. This is an example of a grade 3 tumor. Other histologic features were present elsewhere in the sample.

Syncytial Architecture

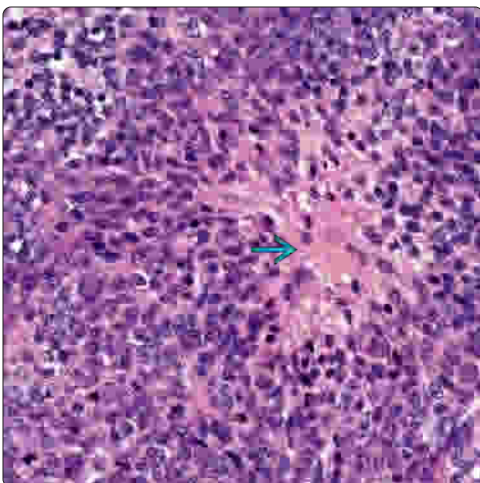


Nuclear Pleomorphism

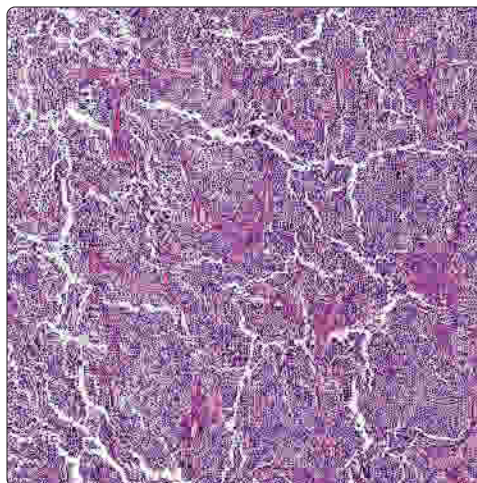



(Left) Within a lobule, the neoplastic cells have a high nuclear to cytoplasmic ratio, nuclear hyperchromasia, and a suggestion of pseudorosettes. This tumor shows a syncytial architecture. (Right) It is not uncommon in a single tumor to have a number of different appearances, in which the cells become slightly larger (center) than the remaining cells, a finding seen more commonly in higher grade tumors.

Homer Wright Pseudorosette



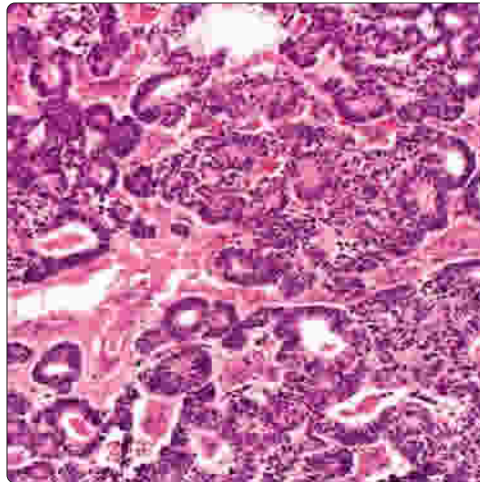
Cracking Artifacts



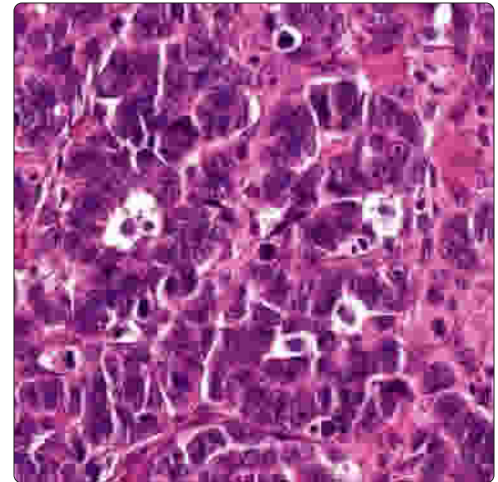
(Left) A pseudorosette (Homer Wright type) shows a peripheral palisade of neoplastic cells cuffing a finely fibrillary neural matrix material in the center . This pseudorosette is seen in up to 30% of grade 1 and 2 tumors. (Right) There is still a vague lobular architecture in this ONB. There is often a cracking artifact, which can accentuate the lobular architecture.

(Left) True rosettes (of Flexner-Wintersteiner) have gland-like, tight annular formations with secretions or concretions in the lumen. The cells lining these duct-like spaces are nonciliated columnar cells. These rosettes are present in ~ 5% of grade 3 or 4 tumors. **(Right)** This grade 3 tumor shows a number of gland-like structures, but a true lumen with the cells arranged around the periphery is not present in this case. There is significant nuclear pleomorphism and prominent nucleoli.

Flexner-Wintersteiner True Rosette

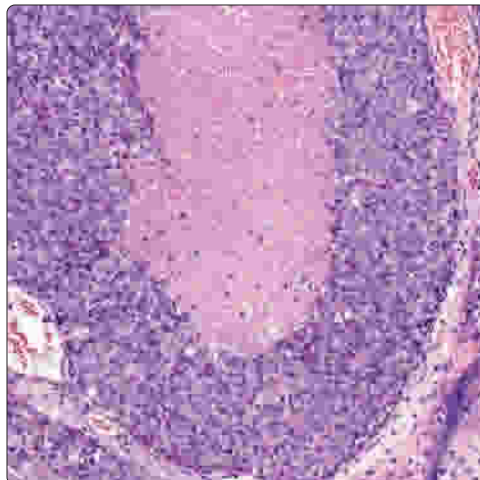


Grade 3 ONB

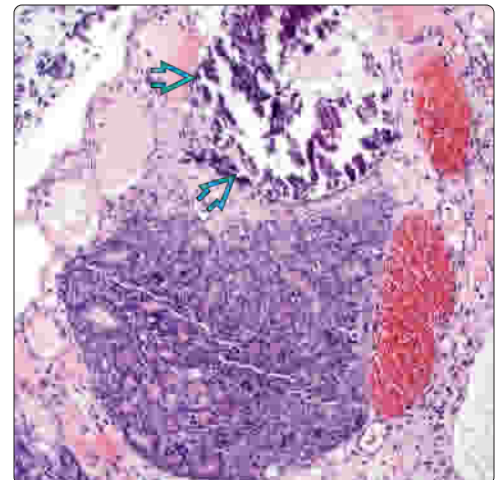


(Left) Coagulative-type necrosis is present in the center of this lobule of tumor. This is a pattern of growth that would be seen in a grade 3 or 4 ONB. **(Right)** This grade 3 tumor shows a number of gland-like structures, with a true lumen, while also showing pseudorosettes. There is significant nuclear pleomorphism. Note the calcification (blue box), present in this case.

Comedonecrosis

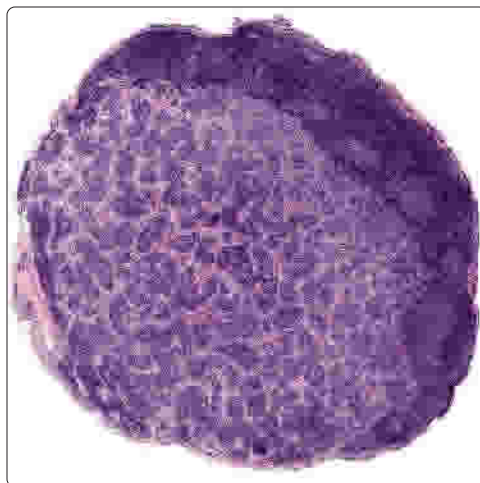


Tumor Calcification

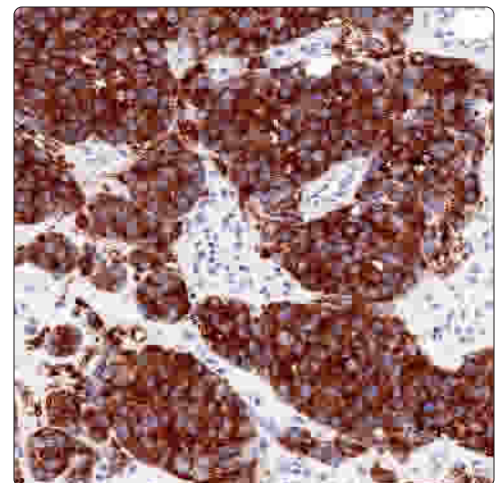


(Left) A cervical lymph node metastasis with nearly 7/8 of the lymph node replaced by the neoplasm is shown. The metastatic foci recapitulate the primary, maintaining a lobular architecture and a richly vascularized stroma. **(Right)** A wide variety of neuroendocrine markers can be applied to highlight the neoplastic cells. Synaptophysin often gives a very strong, heavy chromogen deposition in the neoplastic cells, as illustrated here. There is a slight granularity to the staining pattern.

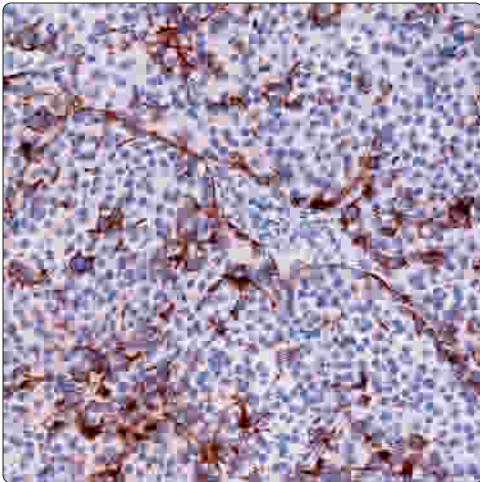
Cervical Lymph Node Metastasis



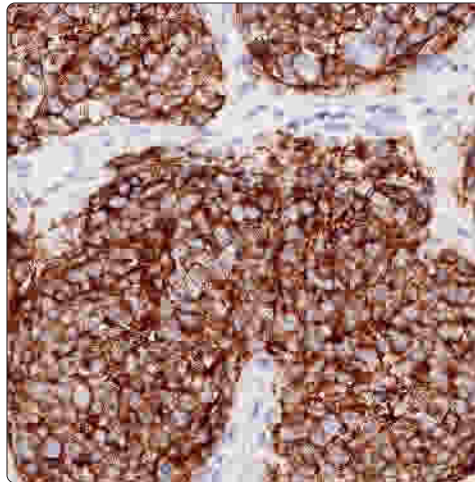
Strong Synaptophysin Reaction



S100 Protein Sustentacular Reaction

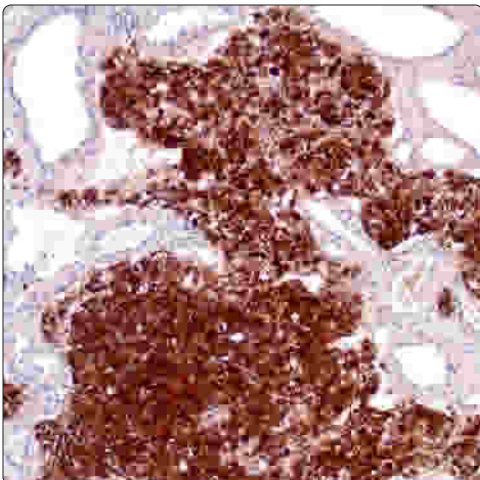


CD56 Membrane Reaction

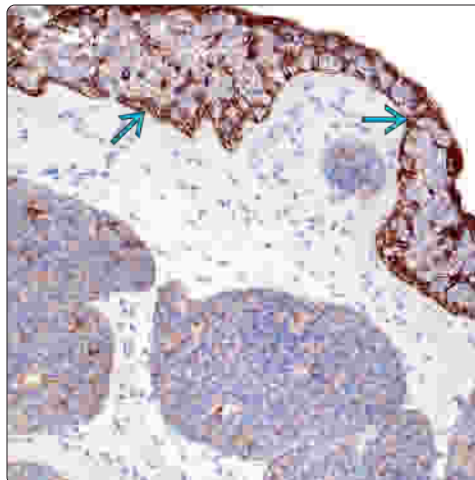


(Left) The peripheral sustentacular cells are highlighted with S100 protein (or GFAP). This pattern of reactivity supports the notion that the various cellular components of olfactory epithelium are all present in the tumor. (Right) CD56 yields a very strong and diffuse membranous and cytoplasmic reaction in the ONB cells. It is important to remember that CD56 is also reactive in rhabdomyosarcoma and NK-/T-cell lymphoma, nasal-type tumors that are included in the differential diagnosis.

Calretinin Positive



CK-PAN May Weakly Stain Tumor Cells

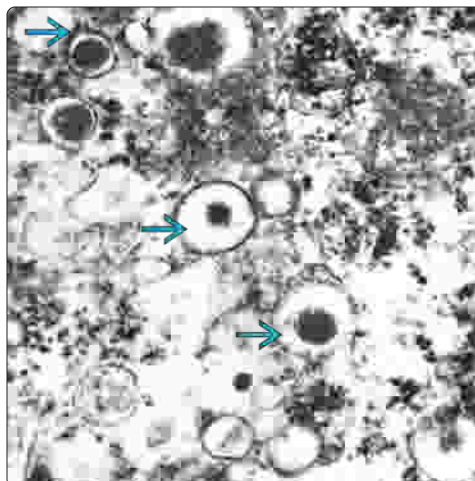


(Left) Strong and diffuse nuclear and cytoplasmic reaction in the neoplastic cells of an olfactory neuroblastoma is shown. This finding can help separate various tumors in the differential diagnosis. (Right) The surface epithelium acts as an internal control for the CK-PAN. Note the rare, isolated, and weak reactivity within the ONB cells with the stroma and also within the surface epithelium.

Grimelius Stain for Neurosecretory Granules



Electron Microscopy of Neurosecretory Granules



(Left) The neurosecretory granules can be highlighted in the neoplastic cells by applying silver stains, with the Grimelius stain illustrated. (Stain courtesy L. Grimelius, MD.) (Right) A poorly differentiated olfactory neuroblastoma shows distinct halos around the dense core granules in the neuroendocrine cells by ultrastructural examination.

Malignant Mucosal Melanoma

KEY FACTS

CLINICAL ISSUES

- Wide age range, usually in 5th-8th decades
- Anterior nasal septum > maxillary sinus
- Wide local excision is treatment of choice, followed by adjuvant radiation
- 5-year disease-free survival < 20%

MACROSCOPIC

- Most are polypoid, with surface ulceration/erosion common
- Range up to 6 cm; mean: 2-3 cm

MICROSCOPIC

- Protean histology, mimic of many other primary tumor types
- Junctional activity and epidermal migration (pagetoid spread) help to confirm primary tumor
- Many patterns of growth
 - Peritheliomatous: Distinctive and unique for STMMM

- Variety of cell types can be seen
 - Undifferentiated, epithelioid, polygonal, small cell, plasmacytoid, rhabdoid, giant cell
- Prominent, irregular, brightly eosinophilic, enlarged nucleoli
- Intracellular cytoplasmic inclusions usually present
- Melanin-containing tumor cells can be seen

ANCILLARY TESTS

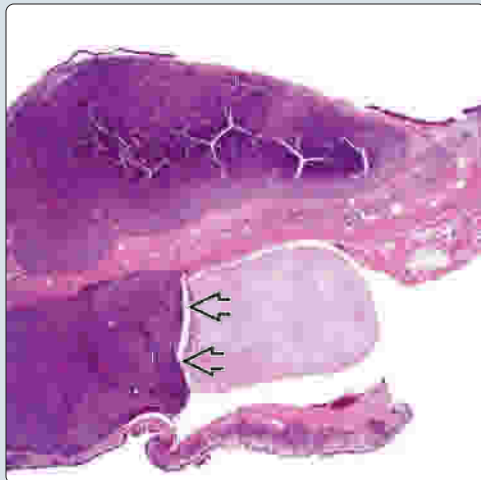
- **Positive:** S100 protein, SOX10, HMB-45, Melan-A, tyrosinase, vimentin

TOP DIFFERENTIAL DIAGNOSES

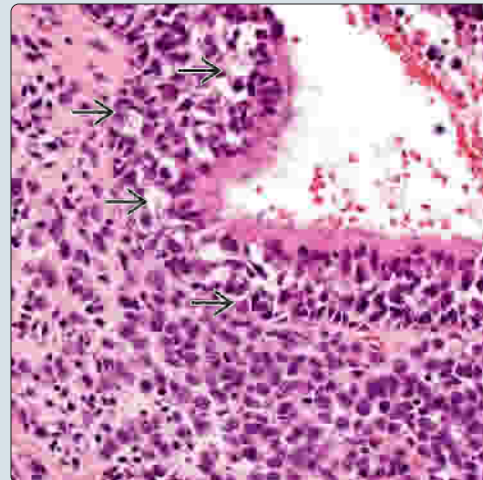
- Olfactory neuroblastoma
- Sinonasal undifferentiated carcinoma
- Rhabdomyosarcoma
- Meningioma
- Leiomyosarcoma, biphenotypic sinonasal sarcoma
- Multiple myeloma (sometimes lymphoma)
- Melanotic neuroectodermal tumor of infancy

Cartilage Destruction by Melanoma

(Left) The nasal septum cartilage is being destroyed by the infiltrative neoplasm. The tumor forms a thick, sheet-like distribution. No pattern of growth can be seen at this magnification, although ulceration is present. **(Right)** Neoplastic, atypical junctional melanocytes are noted within the respiratory epithelium, arranged in a pagetoid spread. The tumor cells are also present within the stroma. This change helps to confirm a primary tumor.

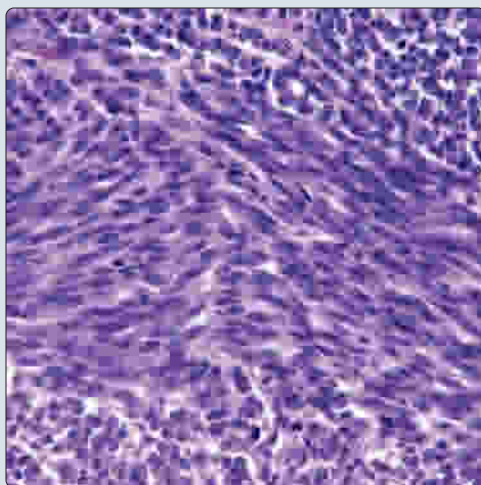


Junctional Melanoma Confirms Primary

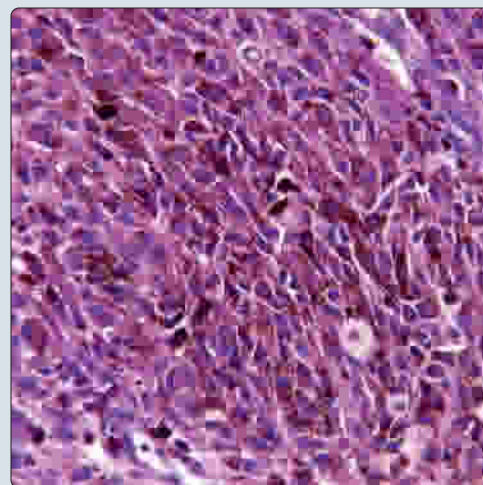


Spindled Cells

(Left) The neoplastic cells are arranged in a short fascicular architecture, comprised of spindled cells. Nucleoli are quite prominent. **(Right)** Hematoxylin and eosin shows a spindled to polygonal population of highly atypical, pigmented neoplastic cells. These changes are characteristic for a pigmented melanoma. The pigment must be within the atypical cells (rather than histiocytes) to qualify as a pigmented melanoma.



Pigmented Melanoma



TERMINOLOGY

Definitions

- Neural crest-derived neoplasms originating from melanocytes and demonstrating melanocytic differentiation

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Formalin, possibly radiation, &/or UV exposure

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare
 - Represents < 1% of all melanomas
 - < 5% of all sinonasal tract neoplasms
 - 15-20% of all skin melanomas occur in head and neck
 - Sinonasal tract and nasopharynx mucosal malignant melanoma (STMMM) represent < 4% of all head and neck melanomas
- Age
 - Wide range, usually in 5th-8th decades
- Sex
 - Equal gender distribution
- Ethnicity
 - Increased incidence in Japanese patients

Site

- ~ 15-20% of melanomas arise in head and neck
 - 80% are cutaneous in origin
 - Ocular origin account for majority of remaining malignant mucosal melanoma (MMM)
 - Sinonasal tract is next most common site
- Anterior nasal septum > maxillary sinus

Presentation

- Nasal obstruction
- Epistaxis or nasal discharge
 - Melanorrhea: Black-flecked (melanin) discharge
- Polyp
- Pain is uncommon

Treatment

- Options, risks, complications
 - Metastatic melanoma to sinonasal tract can develop but is vanishingly rare
 - Breslow thickness and Clark level are not used in sinonasal tract
- Surgical approaches
 - Wide local excision is treatment of choice
- Radiation
 - Adjuvant postoperative radiation therapy may improve locoregional control but does not affect survival

Prognosis

- Poor overall
- 5-year survival: 17-47%
 - 5-year disease-free survival: < 20%
- Recurrences are common

- Poor prognosis associated with
 - Obstruction as presenting symptom; nasopharynx or mixed site of involvement; tumor \geq 3 cm; undifferentiated histology; high mitotic count; recurrence; stage of tumor
- Tyrosine kinase inhibitors may work when proto-oncogene KIT mutations are detected

IMAGING

Radiographic Findings

- Usually identifies extent of tumor and bone invasion
- PET tends to show posterior nasal cavity and sinus tumors better than anterior nasal tumors
- Locoregional and metastatic disease can be detected

MACROSCOPIC

General Features

- Most are polypoid
- White to gray, brown, or black
- Surface ulceration/erosion is common

Size

- Range up to 6 cm; mean: 2-3 cm

MICROSCOPIC

Histologic Features

- Protean histology, mimic of many other primary tumor types
- Junctional activity and epidermal migration (pagetoid spread) help to confirm primary tumor
- Surface ulceration is common, obscuring in situ component
- Bone or soft tissue invasion is common
- Many patterns of growth
 - Peritheliomatous: Distinctive and unique for STMMM
 - Epithelioid, solid, organoid, sheets, nests, papillary structures
 - Fascicles and interlacing bundles, storiform, hemangiopericytoma-like
 - Meningothelial
- Variety of cell types can be seen
 - Undifferentiated
 - Epithelioid, polygonal
 - Small cell, plasmacytoid, rhabdoid, giant cell
- Vesicular nuclei, although sometimes hyperchromatic
- Prominent, irregular, brightly eosinophilic, enlarged nucleoli
- Intranuclear cytoplasmic inclusions usually present
- Melanin-containing tumor cells can be seen
- Tumor cell necrosis is common
- Mitotic figures, including atypical forms, usually easily found and increased
- Inflammation may be present but not of consequence
- Desmoplastic type fibrosis can be seen, but is not common
- Perineural invasion, when present, is poor prognostic indicator
- Tumor depth of invasion (Clark) impossible to accurately assess
- Tumor thickness (Breslow) not meaningful in sinonasal tract

Malignant Mucosal Melanoma

Lymphatic/Vascular Invasion

- Usually present but difficult to assess

Margins

- Difficult to assess, as samples are frequently fragmented and removed piecemeal

ANCILLARY TESTS

Histochemistry

- Fontana-Masson: Melanin bleach confirms melanin in cytoplasm

Immunohistochemistry

- **Positive:** S100 protein, HMB-45, Melan-A, SOX10, microphthalmia transcription factor (MITF), tyrosinase, vimentin
- p16 expression is lost in most MMM (74%) but is **not** correlated with worse prognosis

Genetic Testing

- Comparative genomic hybridization (CGH) shows chromosome arm 1q is gained in nearly all tumors studied
- Gains of 6p (93%) and 8q (57%) are also identified
- Proto-oncogene KIT can be assessed in metastatic mucosal melanomas, therapeutic target for tyrosine kinase inhibitors
 - BRAF is **not** usually assessed in setting of MMM (< 10% harbor mutations)

Electron Microscopy

- Premelanosomes and melanosomes confirms melanocytic origin

DIFFERENTIAL DIAGNOSIS

Olfactory Neuroblastoma

- Lobular architecture
- Fibrillary matrix material associated with rosettes and pseudorosettes
- **Positive:** CD56, chromogranin, synaptophysin, and sustentacular S100 protein

Sinonasal Undifferentiated Carcinoma

- Small cells with high nuclear:cytoplasmic ratio
- Necrosis, destructive growth, and vascular invasion
- **Positive:** Strong, diffuse keratin; **negative:** Melanoma markers

Rhabdomyosarcoma

- Tends to develop in younger patients (although not alveolar type)
- Nests, alveolar patterns are similar
- Strap and rhabdoid patterns are helpful
- Cross striations can confirm diagnosis
- **Positive:** Desmin, MYOD1, myogenin, SMA, MSA, CD56

Meningioma

- Usually secondary in sinonasal tract from intracranial primary
- Meningothelial pattern, spindled cells with intranuclear cytoplasmic inclusions
- **Positive:** EMA, CK7 (prepsammomatous); **negative:** SOX10, S100 protein (usually)

Leiomyosarcoma

- Fascicular architecture, frequently associated with necrosis and high mitotic index
- Perinuclear vacuoles and cigar-shaped nuclei are rare in melanoma
- **Positive:** Muscle markers; **negative:** Melanoma markers

Biphenotypic Sinonasal Sarcoma

- Poorly circumscribed, invasive, cellular spindle cell tumor with epithelial inclusions and low mitoses
- **Positive:** S100 protein, SMA, MSA; **negative:** SOX10, HMB45, Melan-A, tyrosinase

Plasma Cell Myeloma (Plasmacytoma)

- Hematologic neoplasm giving sheet-like pattern of plasmacytoid cells
- Hof zone, paranuclear clearing, and rounded nuclei with clock face-like chromatin distribution
- **Positive:** CD138, CD79a, κ or λ , and other hematologic markers
- Lymphoma is uncommonly in the differential diagnosis

Melanotic Neuroectodermal Tumor of Infancy

- Tumor of neonatal period, affecting gnathic bones
- Biphasic tumor with small and large cells, with pigment easily identified

Metastatic Melanoma

- While theoretic consideration, junctional/pagetoid spread helps to exclude this possibility
- Clinical and radiographic examinations are only way to make definitive separation

Mesenchymal Chondrosarcoma

- Small, undifferentiated cell appearance, but if enough sections are taken, cartilaginous features can be seen
- **Positive:** S100 protein (chondrocytic tumors are positive); **negative:** HMB-45, tyrosinase, Melan-A

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10. Prasad ML et al: Clinicopathologic differences in malignant melanoma arising in oral squamous and sinonasal respiratory mucosa of the upper aerodigestive tract. *Arch Pathol Lab Med*. 127(8):997-1002, 2003
11. Thompson LD et al: Sinonasal tract and nasopharyngeal melanomas: a clinicopathologic study of 115 cases with a proposed staging system. *Am J Surg Pathol*. 27(5):594-611, 2003

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
S100	Positive	Nuclear & cytoplasmic	Diffuse and strong stain usually; identified in about 90% of cases
HMB-45	Positive	Cytoplasmic	Variably reactive in most cases (~ 75%)
SOX10	Positive	Nuclear	Strong and diffuse in nearly all tumor cells
Tyrosinase	Positive	Cytoplasmic	Variably reactive in most cases (~ 75%)
Melan-A103	Positive	Cytoplasmic	Variably reactive in majority of cases (~ 66%)
MITF	Positive	Nuclear	Positive in majority of cases (~ 55%)
NSE	Positive	Cytoplasmic	Positive in < 50% of tumor cells, often focal
CD117	Positive	Cytoplasmic	Positive in ~ 33% of cases
CD99	Positive	Cytoplasmic	Positive in ~ 25% of cases
Vimentin	Positive	Cytoplasmic	All tumor cells
CD56	Positive	Cell membrane & cytoplasm	~ 7% of cases
Synaptophysin	Positive	Cytoplasmic	Nonspecific in ~ 10% of cases
EMA	Positive	Cytoplasmic	< 5% of tumor cells
Chromogranin-A	Negative		
CD45RB	Negative		
CK-PAN	Negative		
GFAP	Negative		
Actin-HHF-35	Negative		
Actin-sm	Negative		
Desmin	Negative		
MYOD1	Negative		

Mucosal Melanoma of the Head and Neck

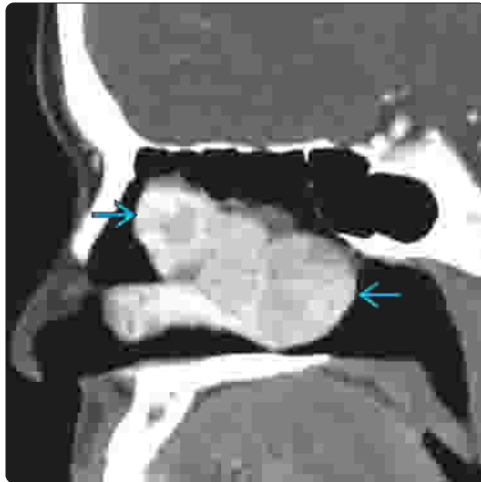
Classification	Description
Primary tumor (T)	
T3	Mucosal disease only
T4a	Moderately advanced disease (deep soft tissue, cartilage, bone, skin)
T4b	Very advanced disease (brain, dura, skull base, lower cranial nerves [IX, X, XI, XII], masticator space, carotid artery, prevertebral space)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Regional lymph node metastases
Distant metastasis (M)	
M0	No distant metastases
M1	Distant metastasis
Prognostic groups	
III	T3 N0 M0
IVA	T4a N0 M0
	T3-T4a N1 M0
IVB	T4b, Any N M0
IVC	Any T, Any N, M1

AJCC Staging, 7th edition.

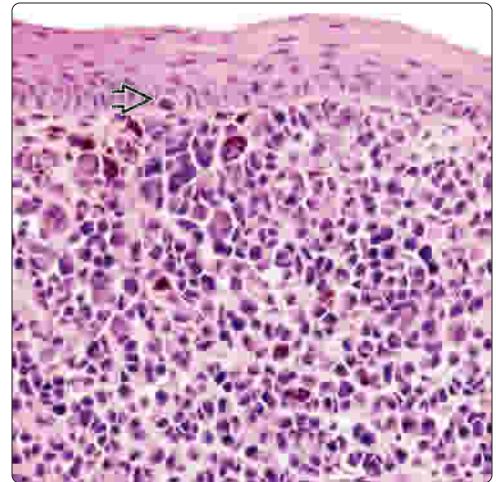
Malignant Mucosal Melanoma

Computed Tomography of Melanoma

(Left) This coronal view of the nasal cavity and sinuses demonstrates a large, polypoid mass arising from and destroying the cartilage of the septum. These findings are nonspecific for a melanoma. (Right) Isolated junctional neoplastic cells are noted in this malignant mucosal melanoma (MMM). The neoplastic cells in the stroma show pleomorphism and a plasmacytoid appearance, identical to the junctional cells. Pigment is easily identified.

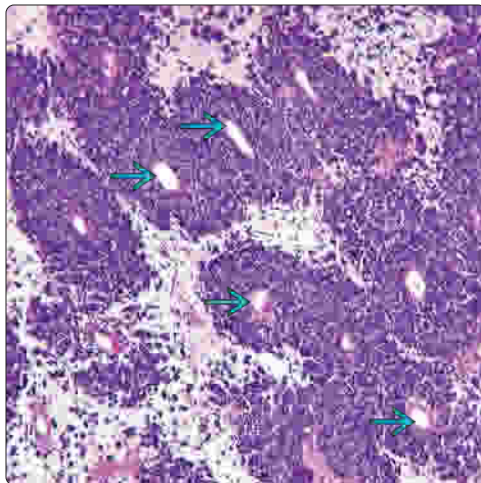


Junctional or Pagetoid Spread

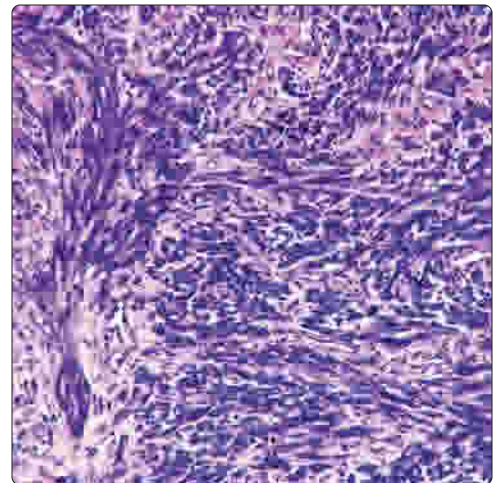


Peritheliomatous Pattern

(Left) This peritheliomatous or perivascular distribution of the neoplastic cells is quite characteristic for a melanoma. It is thought to represent viable tumor cells remaining around vessels. This pattern can be seen in other tumors but not to the same frequency as it is in melanoma. (Right) MMM can be arranged in a number of different architectures, with a fascicular architecture seen here. The spindle cells are arranged in short, intersecting fascicles. The cells are somewhat syncytial in appearance.

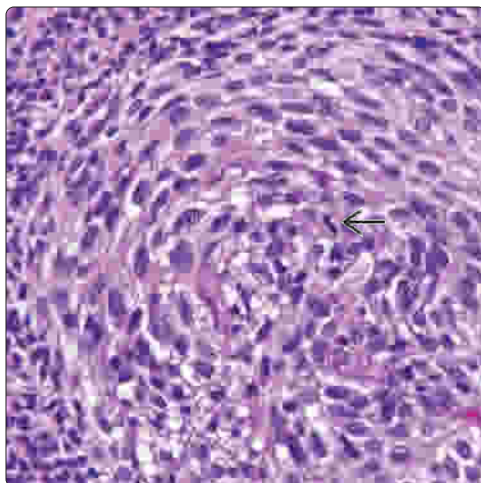


Fascicular Architecture in Melanoma

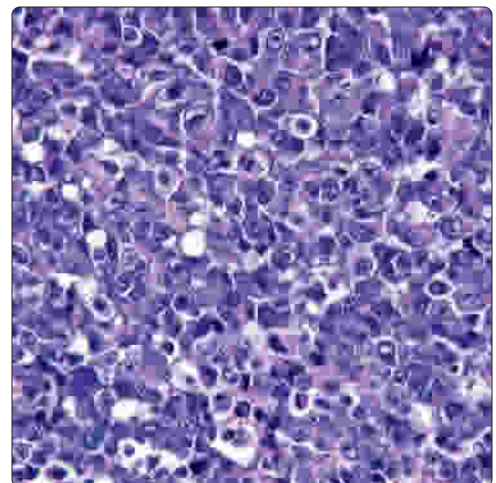


Meningothelial Pattern

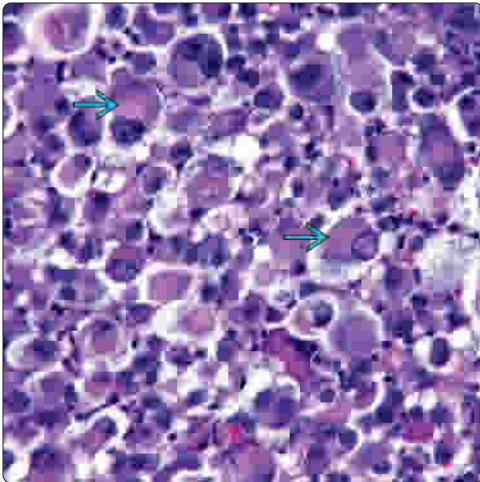
(Left) There is a whorled, meningothelial pattern to this melanoma. This pattern can mimic a meningioma. S100 protein can be positive in both lesions, although, SOX10 and HMB45 are negative in meningioma. Note the mitosis. (Right) It is not uncommon to have an undifferentiated or small round blue cell appearance to MMM. There is a slightly plasmacytoid appearance to the cells. Note the very prominent nucleoli. Pigment is absent.



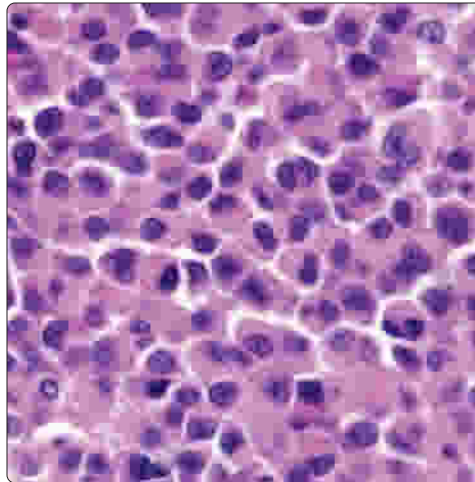
Undifferentiated Cytology Pattern



Plasmacytoid Cytology

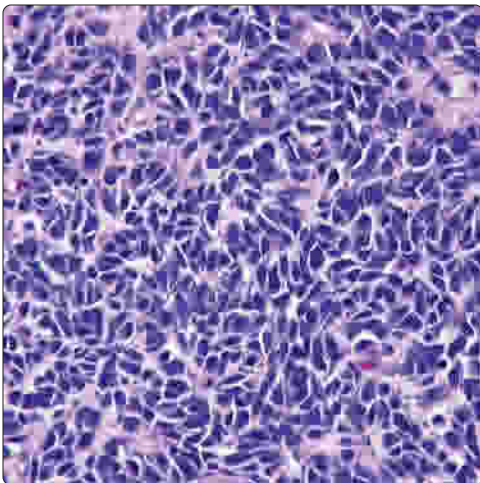


Rhabdoid Cytology

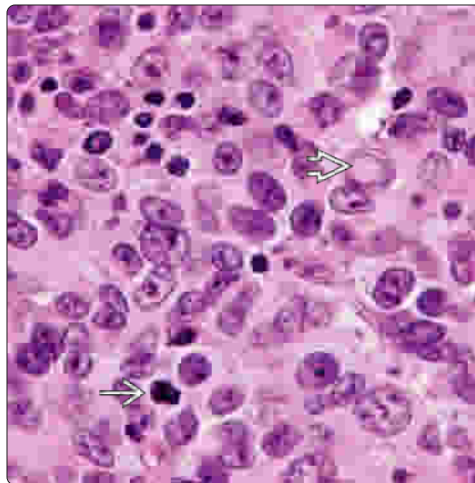


(Left) This tumor shows a very pronounced plasmacytoid appearance, including a Hofmann zone adjacent to the nucleus [B]. There are intranuclear cytoplasmic inclusions as well as binucleation in this MMM. **(Right)** A rhabdoid appearance with darkly opacified, eosinophilic cytoplasm is the dominant pattern in this MMM. Nucleoli are not as enlarged. Mitotic figures, necrosis, and pigment are not appreciated.

Solid Sheet of Undifferentiated Cells

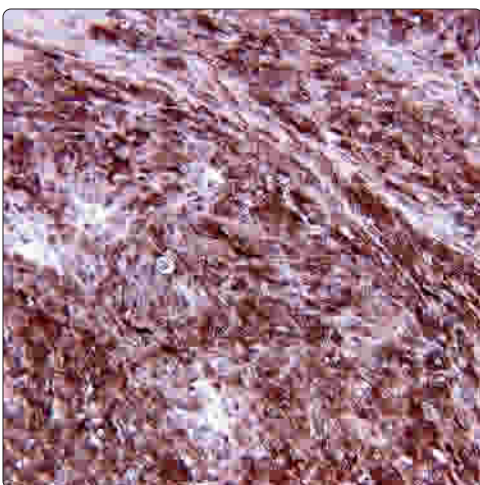


Pleomorphic Cells With Intranuclear Cytoplasmic Inclusion

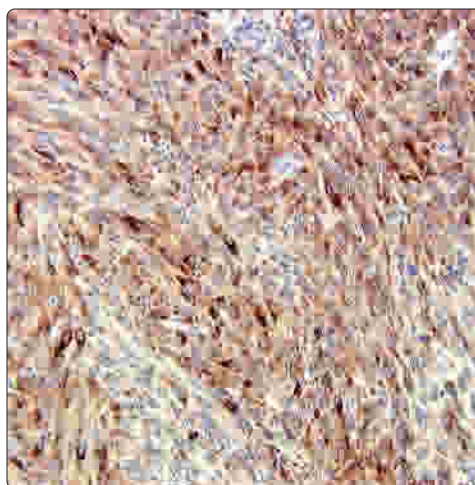


(Left) There is a sheet-like pattern of undifferentiated neoplastic cells in this melanoma. There is a high nuclear:cytoplasmic ratio, but other characteristic histologic features are absent. Immunohistochemistry is most helpful in this setting. **(Right)** Pleomorphic polygonal cells comprise this melanoma. There is remarkable variability between cells. Prominent, eosinophilic nucleoli are noted, along with intranuclear cytoplasmic inclusions [B]. Mitotic figures are also noted [C].

S100 Protein Positive Reaction



Tyrosinase Positive Cells



(Left) Positive S100 protein is immunoreactive in this spindle cell melanoma. There is both cytoplasmic and nuclear reactivity with this marker that highlights nearly all of the cells. **(Right)** The neoplastic cells show a strong and diffuse cytoplasmic reaction with tyrosinase in this spindle cell melanoma. A spindle tumor has a broad differential in this location, with IHC helping to reach a definitive diagnosis.

Ewing Sarcoma, Including Sinonasal Adamantinoma-Like

KEY FACTS

TERMINOLOGY

- High-grade primitive malignant small, round tumor cell sarcoma with variable neuroectodermal differentiation defined by presence of translocation involving *EWSR1* gene

CLINICAL ISSUES

- ~ 10% of Ewing sarcomas (EWS) occur in head and neck
- ~ 80% of tumors develop in < 20 year olds
- Slight male predilection
- Maxillary sinus > nasal fossa > turbinates
- Multimodality therapy (chemotherapy, radiation, and surgery) achieves best outcome
 - Overall, 70% event-free 5-year survival
 - ~ 30% have metastases at presentation, which is associated with worse outcome

MICROSCOPIC

- Diffuse, densely cellular tumor
- Coagulative necrosis with high mitotic index

- Uniform, small to medium round cells with scant, vacuolated cytoplasm
- Nuclei are round with dispersed fine chromatin distribution and small nucleoli

ANCILLARY TESTS

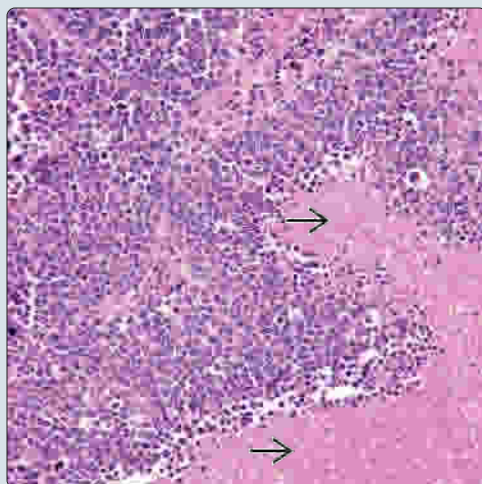
- PAS with diastase identifies glycogen
- CD99 (membrane & cytoplasm), FLI-1 and ERG (nuclear) nearly always positive
- FISH or RT-PCR for t(11;22)(q24;q12) (*EWSR1/FLI1*) fusion product
 - *ERG*, *ETV1*, *ETV4*, *FEV* may be translocation partners

TOP DIFFERENTIAL DIAGNOSES

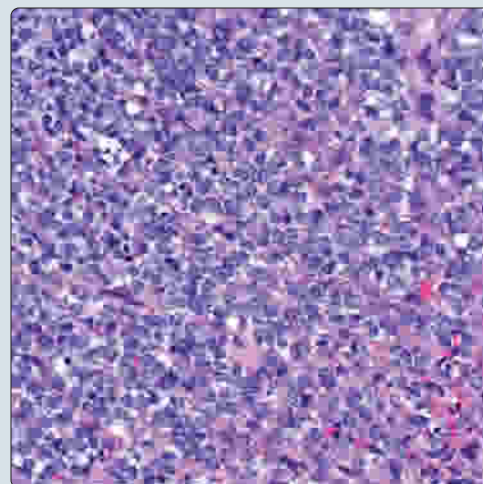
- Olfactory neuroblastoma, lymphoma, rhabdomyosarcoma, *NUT* midline carcinoma
- Pituitary adenoma, mesenchymal chondrosarcoma, osteosarcoma (small cell type), sinonasal undifferentiated carcinoma, mucosal melanoma

Coagulative Necrosis

(Left) There is a very cellular tumor arranged in a diffuse, sheet-like pattern. Note the isolated fibrous connective tissue septa. Areas of coagulative and geographic necrosis are seen [2]. There is often peritheliomatous tumor sparing. (Right) There is a diffuse, sheet-like distribution of primitive neoplastic cells in this Ewing sarcoma (EWS). There are small nucleoli in a syncytial distribution of the neoplastic cells.

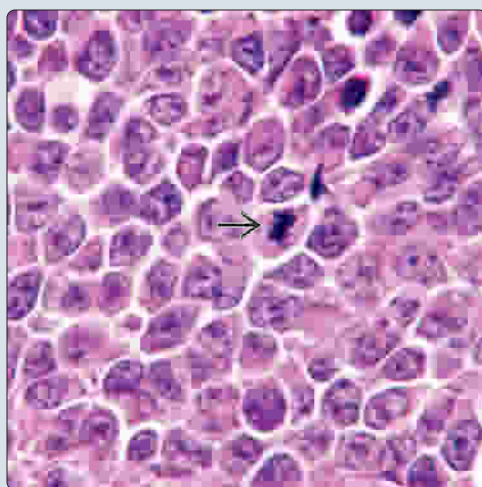


Diffuse Growth of Immature Cells

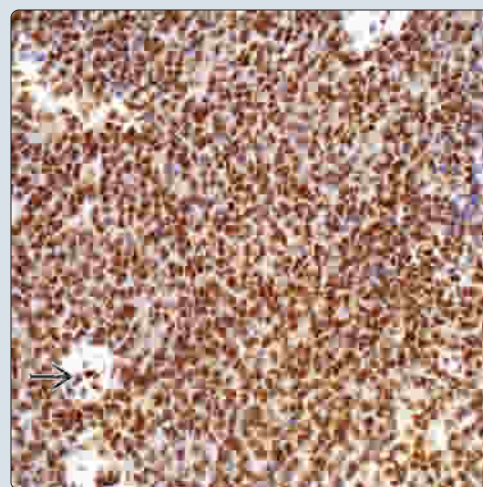


Nucleoli in Neoplastic Cells

(Left) A relatively uniform population of medium cells shows a high nuclear:cytoplasmic ratio. The nuclei are round to slightly irregular with dispersed, fine chromatin distribution and small nucleoli. Note the mitotic figures [2]. (Right) Although not specific, EWS is nearly always strongly and diffusely positive with FLI-1. There is a nuclear reaction. Note the internal control (endothelial cells [2]).



FLI-1 Immunohistochemistry



TERMINOLOGY

Abbreviations

- Ewing sarcoma (EWS)

Synonyms

- Primitive neuroectodermal tumor (PNET) encompasses many tumors
 - Medulloblastoma, medulloepithelioma, olfactory neuroblastoma, retinoblastoma, pineoblastoma, ependymoblastoma, neuroblastoma

Definitions

- High-grade primitive malignant small, round tumor cell sarcoma with variable neuroectodermal differentiation defined by presence of translocation involving *EWSR1* gene
 - EWS and PNET considered on morphologic spectrum, with both expressing similar genetic alterations
 - *EWSR1* or *FUS* rearrangements
 - **Extraskeletal** tumors only considered (Askin tumor and atypical EWS excluded)

ETIOLOGY/PATHOGENESIS

Familial

- Sinonasal EWS has been reported in association with heritable retinoblastoma

Pathogenesis

- Pluripotential mesenchymal &/or neural crest stem cells
- Common neural crest origin with variable neural differentiation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Exceedingly rare
 - Worldwide overall tumor incidence: 2/1,000,000 children
 - ~ 10% of EWS/PNET occur in head and neck
 - ~ 20% of these cases develop in sinonasal tract
- Age
 - Predominantly tumor of children and young adults
 - ~ 80% of tumors develop in < 20 year olds
 - Median: 12 years
 - Older adults uncommonly affected
- Sex
 - Slight male predilection
- Ethnicity
 - Blacks are rarely affected
 - Greater susceptibility in Europeans: Single nucleotide polymorphisms in *TARDBP* and *EGR2*

Site

- Skull and jaws > sinonasal tract > orbit > mucosal sites
 - Sinonasal tract: Maxillary sinus > nasal fossa > > turbinates
- Dura, orbit, or brain extension may be seen

Presentation

- Patients present with pain, mass, teeth mobility, and obstruction

- Bone pain specifically
- Symptoms often develop rapidly within several months

Laboratory Tests

- Elevated serum lactate dehydrogenase helps in managing recurrence

Treatment

- Options, risks, complications
 - Multimodality therapy (chemotherapy, radiation, and surgery) achieves best outcome
 - High-dose myeloablative radiochemotherapy with autologous bone marrow or peripheral blood stem cell rescue is aggressive alternative
- Surgical approaches
 - Wide excision after chemotherapy
- Drugs
 - Multiple neoadjuvant chemotherapeutic agents in combination
 - Vincristine, doxorubicin, cyclophosphamide, and dactinomycin; ifosfamide and etoposide may be used
 - Fenretinide shows promise
- Radiation
 - Used as adjuvant therapy for local disease control

Prognosis

- Overall, 70% event-free 5-year survival
 - Aided by excellent radiographic studies and multimodality therapy
- Head and neck tumors have much better prognosis than tumors in other anatomic sites
- Size and stage are most important prognostic factors
 - Tumors with *EWSR1/FLI1* fusion have better prognosis than less common fusion types
- Intranasal tumors frequently spread into paranasal sinuses
- Up to 30% of patients have metastases at presentation, 1 of the most important prognostic factors, and when present, is associated with worse prognosis
- Common sites of spread
 - Lungs, bone marrow, bone, brain, and lymph nodes
 - Isolated lung metastases may have better outcome
- Unfavorable prognosis associated with
 - Tumor stage, > 8 cm, elevated WBC and sedimentation rate, p53 alterations, filigree microscopic pattern, no response to chemotherapy prior to resection

IMAGING

Radiographic Findings

- Destructive osteolytic lesion with bony erosion
- Periosteal reaction (onion skin) frequently seen
 - Not as common in sinonasal tract tumors as in appendicular skeleton

MACROSCOPIC

General Features

- Tumors are multilobular or polypoid, with a gray-white and glistening cut surface
- Surface mucosal ulceration and hemorrhage

Size

- Range: Up to 6 cm

Ewing Sarcoma, Including Sinonasal Adamantinoma-Like

MICROSCOPIC

Histologic Features

- Diffuse, densely cellular, sheet-like or lobular pattern
- Sheets and large nests of cells with indistinct cell borders
- Coagulative and geographic necrosis is easy to identify
 - Peritheliomatous tumor sparing
- Uniform, small to medium-sized round cells with indistinct borders
- High nuclear:cytoplasmic ratio
- Nuclei are round to oval with dispersed fine chromatin distribution, distinct nuclear membranes, and small nucleoli
- Scant, vacuolated, or cleared pale cytoplasm
- Mitotic figures are increased
- Uncommonly, true rosettes and pseudorosettes may be seen (10% of cases)
 - Interpreted to be neural differentiation
- Prominent intratumoral thin-walled vessels, sometimes compressed

Atypical

- Lobular architecture, alveolar pattern, or increased extracellular matrix
- Increased mitoses (> 2/HPF), pleomorphism, and increased spindle cells (often at tumor margin)
- Lack of glycogen in cytoplasm (PAS stain)

ANCILLARY TESTS

Cytology

- Cellular smears with undifferentiated cells, focal clusters, but predominantly single cells
 - Small round tumor cells with high nuclear:cytoplasmic ratio and scant cytoplasm
 - Pale cytoplasm with cytoplasmic vacuoles
 - Irregular, punched-out cytoplasmic vacuoles due to glycogen
 - Nuclei with fine to smudged chromatin and small, basophilic nucleoli
 - Naked nuclei focally showing crush artifacts (but **not** typically nuclear molding)
- **Absence** of lymphoglandular bodies, cellular dyscohesion, rosettes, eosinophilic fibrillar material, and plasmacytoid cells

Histochemistry

- Diastase-sensitive PAS(+) intracytoplasmic material identifies glycogen

Immunohistochemistry

- CD99 (MIC2, O13, HBA-71, p30/32, 12E7) is nearly always positive
 - CD99 represents monoclonal antibody to *EWSR1/FLI1* fusion product
- FLI-1 and ERG are nearly always positive (sensitive), but nonspecific

Genetic Testing

- Dual-color break-apart probe FISH analysis will confirm translocation
 - Detected in ~ 95% of cases

- Reverse transcriptase-polymerase chain reaction (RT-PCR) detects *EWSR1/FLI1* fusion product and can be performed on paraffin-embedded tissue
 - Chromosomal translocation: t(11;22)(q24;q12) or t(21;22)(q22;q12)
 - Many chimeric *EWSR1/FLI1* transcripts, representing different combinations of exons from *EWSR1* and *FLI1* or *EWSR1* and *ERG*
 - *ERG*, *ETV1*, *ETV4*, *FEV* may be translocation partners
 - *EWSR1* is protooncogene: Present in native cells, but when activated, becomes oncogene
 - *EWSR1* gene aminoterminal domain (22q12) fuses with carboxy-terminal domain of *FLI1* (11q24) to create chimeric protein
- Other translocation partners can also be seen: t(4;19) or t(10;19)

DIFFERENTIAL DIAGNOSIS

Olfactory Neuroblastoma

- Specific anatomic site: Ethmoid sinus (cribriform plate)
- Lobular architecture, with neural matrix, rosettes (true and pseudorosettes)
- In low-grade lesions, mitotic figures and necrosis are absent
- Chromogranin, CD56, synaptophysin (+), with sustentacular S100 protein reactivity; keratin rarely; CD99 (-)

Lymphoma

- Dispersed population without molding or cohesive groups
- Positive with lymphoid markers: CD45RB, CD20, CD3, CD56, based on specific tumor type

Rhabdomyosarcoma

- Slightly plasmacytoid appearance, with eosinophilic perinuclear cytoplasm condensation, strap cells, rich in glycogen
- **Positive:** Myoid markers: Desmin, MYOD1, myogenin, MYF4, myoglobin, actin

Mesenchymal Chondrosarcoma

- Small cell population arranged around hemangiopericytoma-like vessels
- Must submit many sections to see areas of chondroid differentiation

Osteosarcoma, Small Cell Type

- Uncommon tumor type in sinonasal tract, with lacy osteoid matrix

Pituitary Adenoma

- Sphenoid sinus usually affected
- Bland cytology, with sheet-like to lobular architecture
- Various neuroendocrine markers (+) but CD99 absent

Mucosal Malignant Melanoma

- Frequently show mucosal origin (in situ)
- Pleomorphic population, plasmacytoid and spindled cell appearance, intranuclear cytoplasmic inclusions, pigmentation, peritheliomatous distribution
- **Positive:** S100 protein, HMB-45, SOX10, melan-A

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CD99	Positive	Cell membrane and cytoplasm	Nearly all tumor cells with membrane accentuation
FLI-1	Positive	Nuclear	Most tumor cells
ERG	Positive	Nuclear	C-terminus clone (EPR3864(2)) matches <i>EWSR1/Flt-1</i> fusion
SNF5	Positive	Nuclear	All tumor cells
p14	Positive	Nuclear	Nearly all tumor cells
Rb	Positive	Nuclear	Nearly all tumor cells
Vimentin	Positive	Cytoplasmic	Most tumor cells
NSE	Positive	Cytoplasmic	Usually more frequently seen in PNET than EWS
β -catenin-cytoplasm	Positive	Cell membrane & cytoplasm	Majority of tumor cells
PGP9.5	Positive	Cytoplasmic	Most tumor cells
Claudin-1	Positive	Cytoplasmic	~ 50% of cases
CD117	Positive	Cytoplasmic	~ 25% of cases
Synaptophysin	Positive	Cytoplasmic	~ 20% of cases
S100	Positive	Nuclear & cytoplasmic	~ 20% of cases
CK-PAN	Positive	Cytoplasmic	Up to 30% of cases, especially adamantinoma-like tumors
Myogenin	Negative		
WT1	Negative		
GFAP	Negative		

Sinonasal Undifferentiated Carcinoma

- Old age at initial presentation, with midline destruction, vascular invasion, bone invasion, perineural invasion
- Strong, diffuse keratin immunoreactivity

NUT Midline Carcinoma

- Poorly differentiated carcinoma with abrupt keratinization presenting in young patients
- Specific molecular alteration required for diagnosis (NUT IHC or *NUT* rearrangement detected by FISH)

Melanotic Neuroectodermal Tumor of Infancy

- Pigmented tumor of maxilla presenting during neonatal or early childhood
- Large, pigmented epithelioid cells associated with smaller, blue round cells in background stromal reaction

STAGING

Same as Rhabdomyosarcoma



- Staging is according to Clinical Groups of Intergroup Rhabdomyosarcoma Study

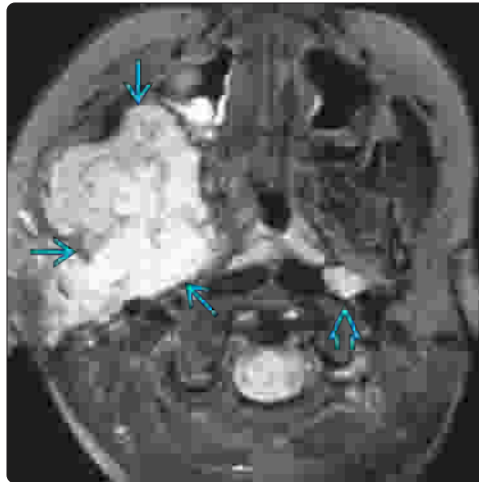
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Ewing Sarcoma, Including Sinonasal Adamantinoma-Like

MR of Heterogenous Tumor



(Left) Axial T2-weighted fat-suppressed MR shows a markedly hyperintense, but heterogeneous, tumor . A prominent left retropharyngeal node  is incidentally noted. This appearance supports the diagnosis of a tumor but is not specific for Ewing. (Right) This is a polypoid, multilobular tumor removed from the nasal cavity of a 28-year-old man. The surface is intact, although, showing areas of erosion and subepithelial hemorrhage. Necrosis is seen as yellow streaks.

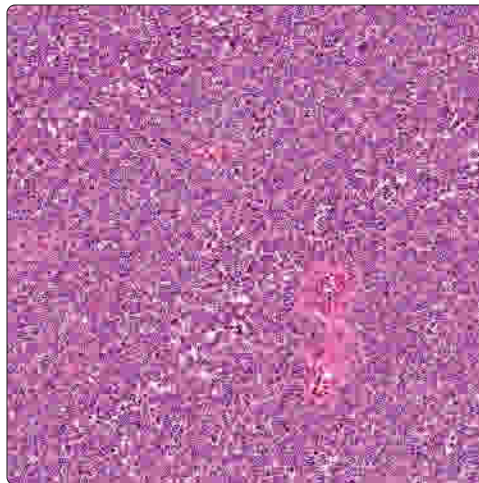


Gross Photograph of Polypoid Tumor

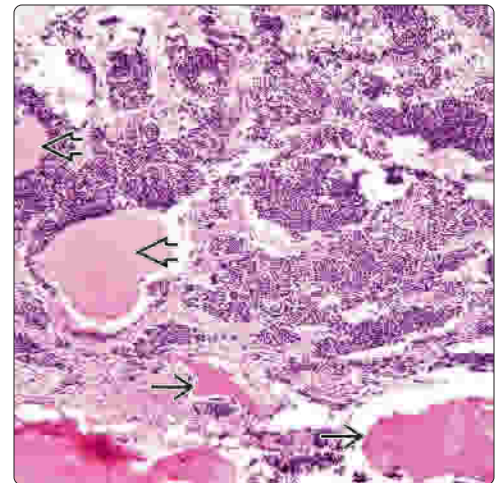


Diffuse Pattern


(Left) There is a diffuse architecture to this EWS. The cells show a high nuclear:cytoplasmic ratio. (Right) Areas of bone invasion are often easy to see . There is a small round blue cell population associated with areas of necrosis  and hemorrhage. This pattern on low power is not specific for EWS but can be seen in a variety of different sinonasal tract tumors.

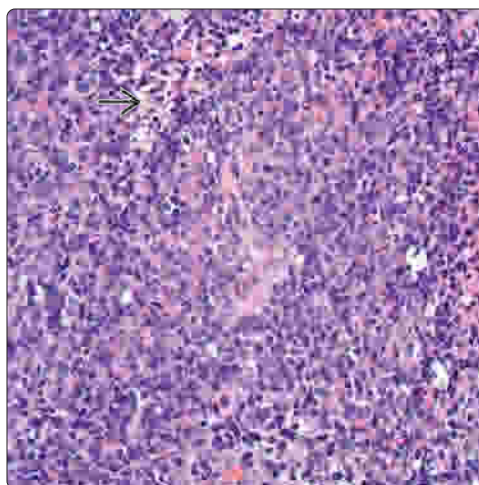


Bone Invasion and Tumor Necrosis

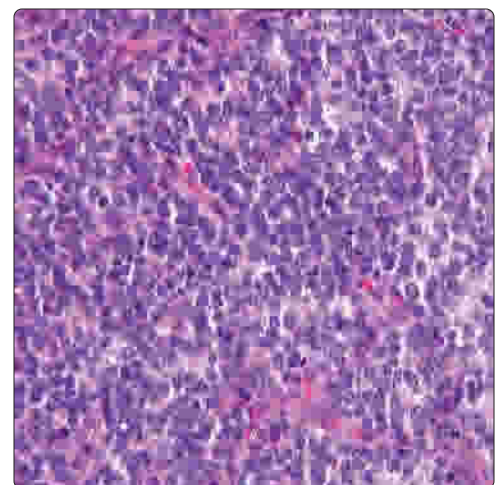


Small Round Blue Cell Population

(Left) There is a monotonous population of small round blue cells that comprise EWS. Areas of degeneration  can be seen, a precursor to necrosis. (Right) There is a vaguely lobular appearance to this monotonous tumor cell population. The cells have round nuclei with delicate nuclear chromatin distribution. Nucleoli are small and inconspicuous. A background vascularity is noted.



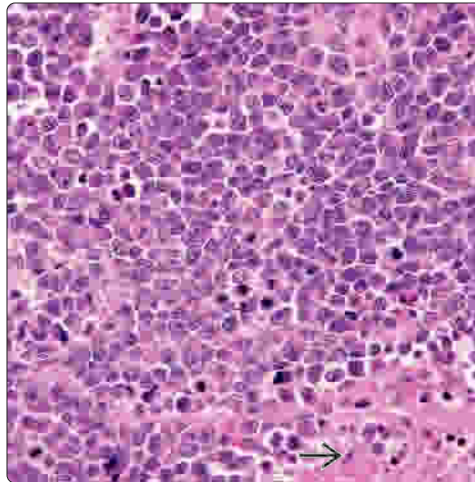
Sheet-Like Distribution





Peritheliomatous Growth With Necrosis

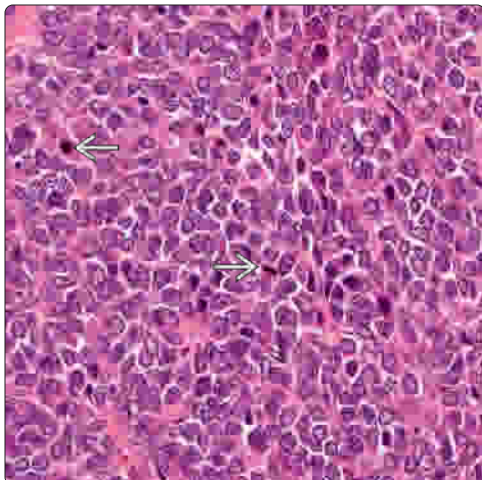


Apoptotic Bodies

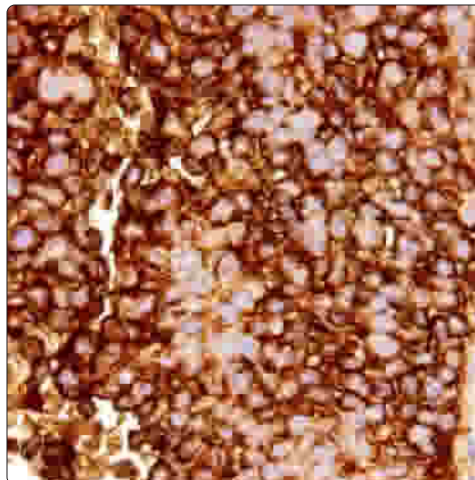



(Left) Vessels are noted in this proliferation of EWS. A small area of comedonecrosis  is easily identified in many tumors. (Right) The cells do not really show distinct cell borders but are arranged in a syncytium. There are areas of coagulative necrosis  and a number of apoptotic bodies and mitotic figures.

Evenly Distributed Chromatin

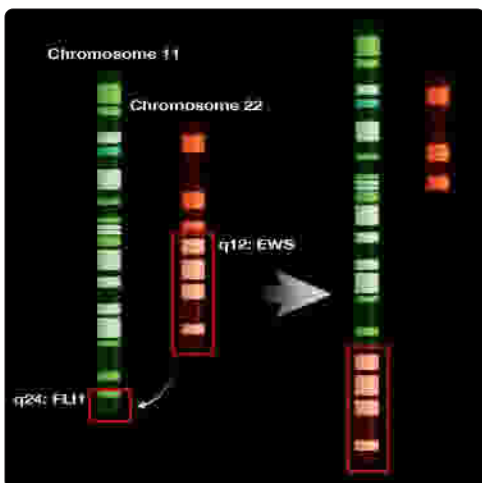


CD99 Immunohistochemistry

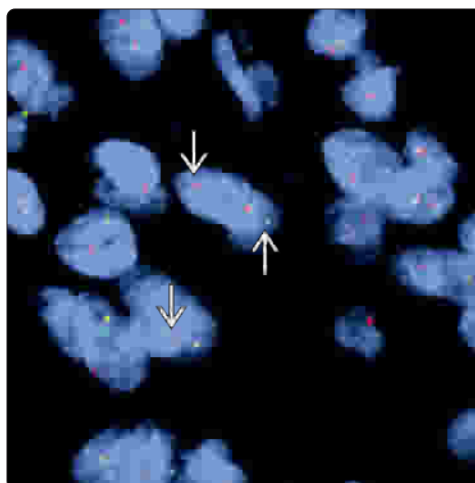



(Left) There is no unique pattern to this sheet of neoplastic cells. The cells have a high nuclear:cytoplasmic ratio, but the cells are small. The nuclear chromatin is evenly distributed. A number of mitotic figures are seen . (Right) There is a strong, diffuse, cytoplasmic reaction with CD99. This type of pattern is not as frequently seen in other tumor types. CD99 is an antibody to the fusion protein between EWSR1 and FLI1.

Graphic of EWSR1 Translocation



FISH Break-Apart Probe for EWSR1



(Left) The characteristic $t(11;22)(q24;q12)$ translocation between the carboxy-terminal domain of FLI1 (11q24) and the EWSR1 gene aminoterminal domain (22q12) creates a fusion product. (Right) A probe that spans the known breakpoints of the EWSR1 gene on chromosome 22 (introns 7-10) is labeled with spectrum green and orange (3' and 5', respectively). With rearrangement, discrete separate red  and green signals are seen instead of the fused yellow signal. (Courtesy A. Nguyen.)

KEY FACTS

TERMINOLOGY

- Complex malignant sinonasal neoplasm with immature and malignant endodermal, mesodermal, and neuroepithelial elements resembling immature teratoma

CLINICAL ISSUES

- Mean age: 54.5 years; range: 0.1-85 years
- Male > Female (7:1)
- Most common sites: High in nasal cavity (72%), ethmoid (55%), maxillary (31%), and sphenoid (19%) sinuses
- Most common symptoms: Nasal obstruction (76%), epistaxis (63%), and headaches (20%)
- Aggressive multimodality therapy (combination of surgery, radiation therapy, and chemotherapy) yields best outcome
 - ~ 30% of patients are dead within 3 years
- Rapid recurrences are common (~ 40%) usually in < 2 years

MACROSCOPIC

- Large, bulky, polypoid, friable, soft, and fleshy masses with necrosis

MICROSCOPIC

- Heterogeneous neoplasm with **intermingled** features of carcinoma, sarcoma, and immature teratoma
 - **Carcinoma** can be squamous or adenocarcinoma
 - **Sarcoma** composed of cartilage, bone, muscle, or fibroblasts in varying degrees of maturation
 - **Neural** elements show primitive neuroepithelial tissue, blastomatous cells, neurofibrillary matrix, and prominent rosettes

TOP DIFFERENTIAL DIAGNOSES

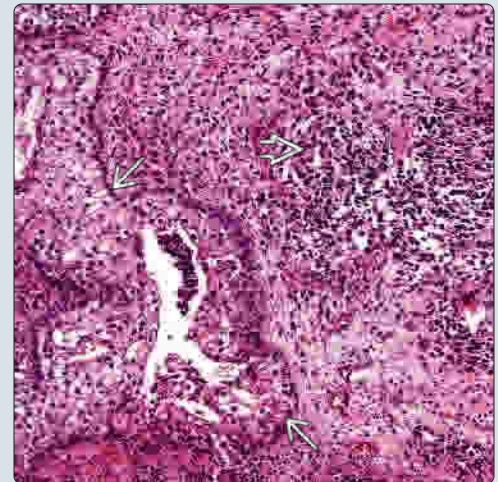
- Olfactory neuroblastoma, rhabdomyosarcoma, sinonasal undifferentiated carcinoma, adenocarcinoma, germ cell tumor, biphenotypic sinonasal sarcoma

Intermingled Adenocarcinoma and Fibrosarcoma

(Left) There is an intimate blending between the adenocarcinoma and the fibrosarcoma in this example of a teratocarcinosarcoma. Immature or primitive elements were seen elsewhere in the sample. (Right) Squamous cell carcinoma with clear cells and well-developed cell borders is surrounded by a cellular immature mesenchyma. The mesenchyma blends into an immature neural matrix. There is no sharp line of demarcation between each of these elements.

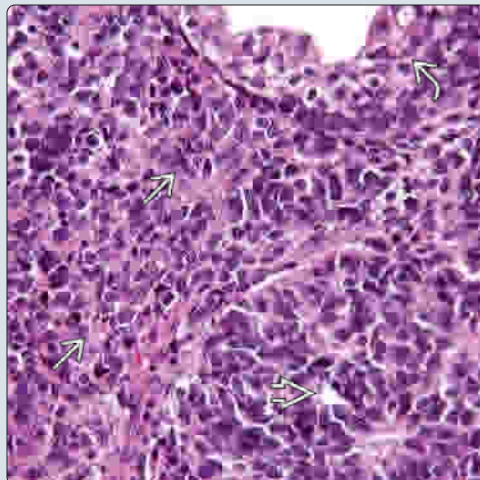


Cleared Squamous Cells and Blastema

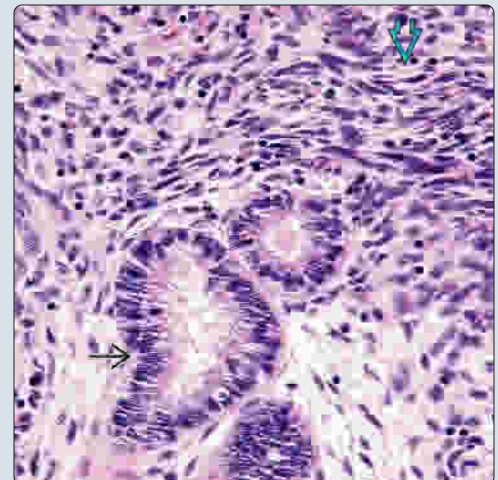


Immature Mesenchymal Elements

(Left) On high power, the immature squamous element is juxtaposed to immature mesenchymal tissue, which is juxtaposed to immature neural tissue, the latter showing a rosette. Note the blending between these elements as they form the tumor. (Right) The adenocarcinoma glandular elements are intimately associated with highly atypical spindled cell elements arranged in a fibrosarcoma pattern.



Adenocarcinoma and Fibrosarcoma Patterns



TERMINOLOGY

Abbreviations

- Sinonasal teratocarcinosarcoma (SNTCS)

Synonyms

- Malignant teratoma
- Blastoma
- Teratocarcinoma
- Teratoid carcinosarcoma
- Mixed olfactory neuroblastoma-craniopharyngioma

Definitions

- Complex malignant sinonasal neoplasm with immature and malignant endodermal, mesodermal, and neuroepithelial elements resembling immature teratoma
- By definition, germ cell tumor is absent (embryonal carcinoma, choriocarcinoma, seminoma, yolk sac tumor)

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Probably arises from primitive cell in olfactory membrane that possess capacity to show multilineage differentiation
- Some consider it germ cell tumor

CLINICAL ISSUES

Epidemiology

- Incidence
 - Extremely rare
- Age
 - Mean: 54.5 years; range: 0.1-85 years
- Sex
 - Male > > female (7:1)

Site

- Most common high in nasal cavity (72%), ethmoid (55%), maxillary (31%), and sphenoid (19%) sinuses
 - Nasopharynx (17%), maxilla (12%), and cribriform plate (12%)
- Frequently involves more than 1 paranasal sinus

Presentation

- Most common symptoms: Nasal obstruction (76%), epistaxis (63%), and headaches (20%)
- Symptoms are usually of short duration (mean: < 4 months)
- May also experience visual changes, anosmia, swelling, pain

Laboratory Tests

- Vasopressin may be ectopically or inappropriately elevated (syndrome of inappropriate antidiuretic hormone [SIADH])

Treatment

- Options, risks, complications
 - Aggressive multimodality therapy (combination of surgery, radiation therapy, and chemotherapy) yields best outcome
 - ~ 40% of patients survive disease free > 3 years; although, ~ 30% of patients die in that time
- Surgical approaches
 - Complete surgical eradication by craniofacial resection, open surgery, or endoscopic resection

- Adjuvant therapy
 - Chemotherapy combined with radiation and surgery in most cases
- Radiation
 - Postoperative radiation

Prognosis

- Guarded prognosis with highly aggressive clinical behavior
 - ~ 30% of patients are dead within 3 years, but ~ 40% alive without evidence of disease (mean: 39 months)
 - Mean: 1.7 years to death
 - Most common cause of treatment failure is local recurrence
 - 40% of patients respond to multimodality therapy
 - Mean survival: 6 years
- Rapid recurrences are common (~ 40%) usually in < 2 years
 - Local paranasal sinus disease, intracranial or orbital extension
- Metastatic disease (~ 20%)
 - Cervical lymph nodes more often than distant metastases (lung)

IMAGING

Radiographic Findings

- Aggressive, poorly marginated, large, soft tissue density mass with bone destruction and invasion across fascial planes
- Best studies: Bone CT and T1WI MR with contrast
 - MR: Soft tissue and neural involvement
 - CT: Bone destruction

MACROSCOPIC

General Features

- Large, bulky, polypoid, friable, soft, and fleshy masses with necrosis

Size

- Mean: > 4 cm

MICROSCOPIC

Histologic Features

- Heterogeneous neoplasm with **intermingled** features of carcinoma, sarcoma, and immature teratoma
 - By definition, germ cell tumor is absent (embryonal carcinoma, choriocarcinoma, seminoma, yolk sac tumor)
- Benign and malignant, immature epithelial, mesenchymal, and neural elements topographically mixed, with transition between elements
 - **Carcinoma** can be squamous or adenocarcinoma
 - Keratinizing or nonkeratinizing squamous epithelium, occasionally cystic
 - Clear cell immature squamous epithelium
 - Pseudostratified columnar, ciliated epithelium
 - Glandular structures with cuboidal or columnar cells, ± mucus production
 - **Sarcoma** composed of cartilage, bone, muscle, or fibroblasts in varying degrees of maturation
 - Spindled, immature mesenchymal cells in matrix (myxoid, mucinous)

Teratocarcinosarcoma

- Cartilage, bone, skeletal, or smooth muscle in embryonal form
- Fibrosarcoma herringbone pattern
- o **Neural** elements show primitive neuroepithelial tissue, blastomatous cells, neurofibrillary matrix, and prominent rosettes
 - Neuronal maturation is rarely seen post chemotherapy

ANCILLARY TESTS

Immunohistochemistry

- Highlights the various constituent elements
 - o Epithelial markers (cytokeratins, CK5/6, EMA, p63)
 - o Spindle cells highlighted with vimentin, GFAP, calponin, desmin, myoglobin, myogenin, actins
 - o Neuroepithelial/blastema elements positive with CD56, chromogranin, synaptophysin, CD99, S100 protein; rarely AFP
- **Negative:** β human chorionic gonadotrophin, neurofilament protein, CD45RB

Genetic Testing

- Trisomy 12 and 1p deletion have been identified

Electron Microscopy

- **Primitive** cells
 - o Neural processes, parallel microtubules, dense core granules
- **Spindle** cells
 - o Actin filaments, skeletal muscle differentiation
- **Epithelial** cells
 - o Desmosomes, intermediate filaments, microvilli, tonofilaments

DIFFERENTIAL DIAGNOSIS

Olfactory Neuroblastoma

- Ethmoid sinus and cribriform plate involvement
- Lobular architecture
- Neurofibrillary matrix, pseudorosettes, and rosettes
- Monotonous small round blue cell neoplasm
- Positive with neuroendocrine markers
- Negative with mesenchymal and epithelial markers (isolated keratin-positive cells can be seen)

Rhabdomyosarcoma

- Embryonal or alveolar types most common in sinonasal tract
- Lacks epithelial and neuroendocrine differentiation (neural tissue)
- **Positive:** Myogenic markers, but also positive with CD56 and keratin (uncommon)

Sinonasal Undifferentiated Carcinoma

- Poorly differentiated epithelial neoplasm, showing destructive midline growth, extensive necrosis, and vascular invasion
- May have rosettes but tends to lack mesenchyma or teratoma-like appearance
- Strong keratin expression, lacking other markers (such as CK5/6)

Adenocarcinoma

- Tumor has epithelial adenocarcinoma elements only
 - o Lacks neural, blastemal, and sarcomatoid elements
- Arranged in distinctive pattern
 - o High- or low-grade sinonasal adenocarcinoma
 - o Salivary gland-type adenocarcinomas (all variants)
 - o Intestinal-type adenocarcinoma tends not to be included in differential consideration

Germ Cell Tumor

- Distinct features of embryonal, choriocarcinoma, seminoma, and yolk sac tumor are not identified in teratocarcinosarcoma
- Unique immunohistochemistry profile helps with separation

Biphenotypic Sinonasal Sarcoma

- Low-grade cellular spindled cell infiltrative neoplasm, often associated with infolded islands of respiratory type epithelium
- While there are neural and myogenic markers positive, true muscle or nerve-type tissues are not identified
- Primitive or blastema (teratoma-like) tissues and epithelial malignancies are not present

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Highly malignant tumor with carcinoma, sarcoma, and teratoma (blastema/primitive) intermingled

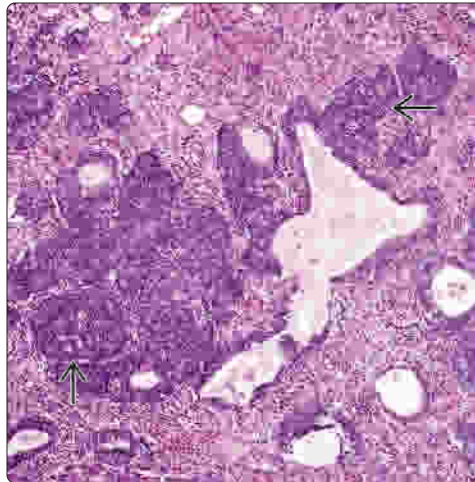
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MR of Heterogenous Sinonasal Tract Mass

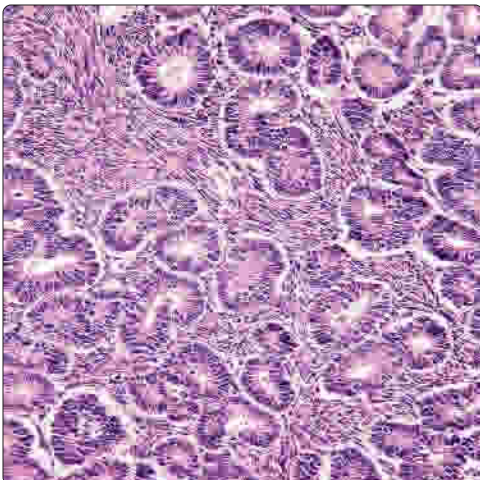


Immature Neural Elements

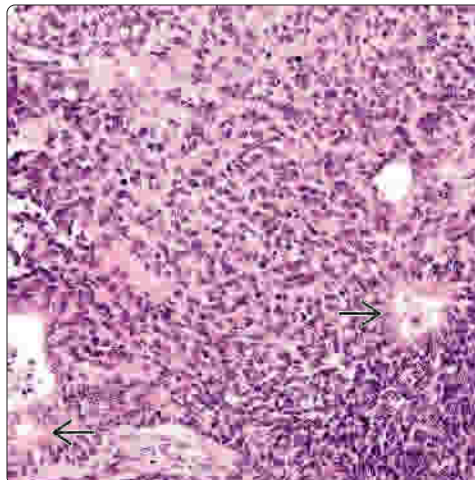


(Left) Axial T1WI MR demonstrates a heterogeneous soft tissue mass, which extensively involves the sinonasal cavities and central skull base. The mass fills the maxillary sinus [arrow], ipsilateral nasal cavity [arrow], and nasopharynx [arrow]. (Right) There is a loosely cellular spindle cell population in the background of this teratocarcinosarcoma. The primitive blastema-neural elements make up the bulk of this tumor, with well-developed rosette formation [arrow].

Glandular-Rosette Formations

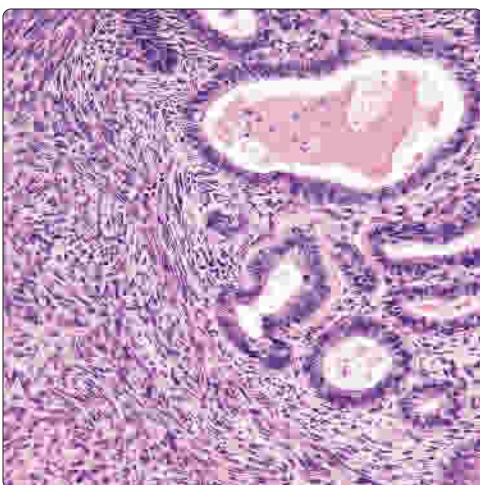


Rosettes Within Blastemal Tissue

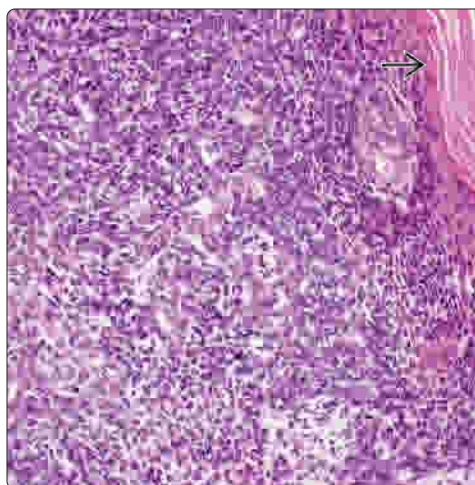


(Left) In a field such as this one, it may be difficult to separate a primitive rosette from a glandular or ductal profile. These structures are intimately associated with the spindled cell sarcoma. (Right) This field shows intermingled features of carcinoma with immature spindled elements (sarcoma) and areas of blastemal tissue (teratoma). There are a number of rosettes [arrow] within this field.

Heterogenous and Mixed Populations



Primitive Squamous and Blastemal Elements



(Left) The heterogeneous nature of the neoplasm shows intermingled features of adenocarcinoma and spindled cell sarcoma in this field. Adenocarcinoma and fibrosarcoma are frequent tumor types. (Right) There is abrupt keratinization [arrow] in this tumor that shows primitive neuroblastoma or mesenchymal elements in the rest of the field. Keratinization and cyst formation are frequently seen in the squamous cell carcinoma portion of a teratocarcinosarcoma.

Fibrosarcoma

KEY FACTS

TERMINOLOGY

- Malignant neoplasm with only fibroblastic &/or myofibroblastic differentiation

CLINICAL ISSUES

- Uncommon sinonasal tract tumor
- Peak age: 5th-6th decades
- Female > male (3:2)
- 1 or more paranasal sinuses (maxillary, ethmoid)
- Present with nasal obstruction and epistaxis
- Recurrences high, especially in incompletely excised tumors
- En bloc resection yields best long-term outcome
- Prognosis generally good with 75% 5-year survival

MICROSCOPIC

- Unencapsulated, often with bone invasion
- Surface epithelial invagination common (~ 1/3)
- Spindled tumor cells arranged in short, compact fascicles at acute angles

- Herringbone or chevron pattern
- Fusiform cells with centrally placed, hyperchromatic, needle-like nuclei with tapering cytoplasm
- Limited pleomorphism and necrosis in most cases
- **Low grade:** Vast majority of tumor; moderate cellularity, limited pleomorphism, few mitoses, no necrosis
- **High grade:** Nuclear pleomorphism, high mitotic activity, scant collagenous stroma, necrosis, and hemorrhage

ANCILLARY TESTS

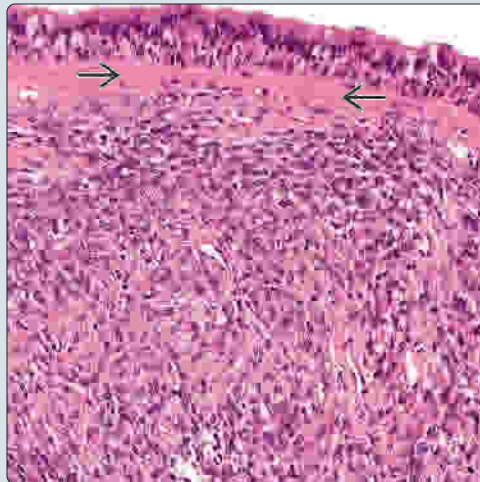
- **Positive:** Strong, diffuse vimentin

TOP DIFFERENTIAL DIAGNOSES

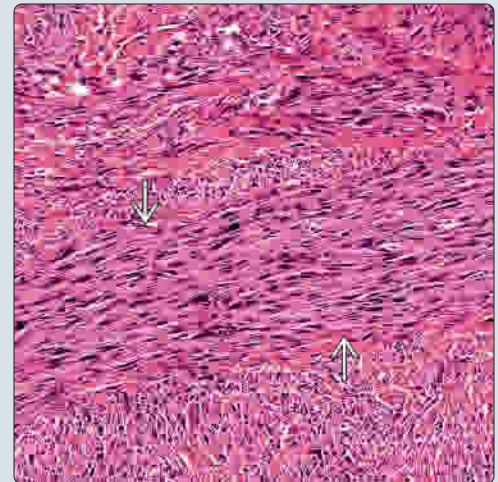
- Inflammatory myofibroblastic tumor, solitary fibrous tumor, glomangiopericytoma, fibromatosis (desmoid type)
- Synovial sarcoma, spindle cell squamous cell carcinoma, melanoma (spindle cell type), malignant peripheral nerve sheath tumor, biphasic sinonasal sarcoma, undifferentiated pleomorphic sarcoma

Separation From Surface Epithelium

(Left) The surface epithelium is separated from the neoplastic proliferation by a Grenz zone of fibrosis. The tumor shows areas of collagenized stroma, but the pattern of growth is difficult to detect from this high-power field. (Right) Unencapsulated tumor demonstrates a moderate to high cellularity, with fascicles showing acute angles. One of the fascicles is perpendicular to the others. There is focal pleomorphism.

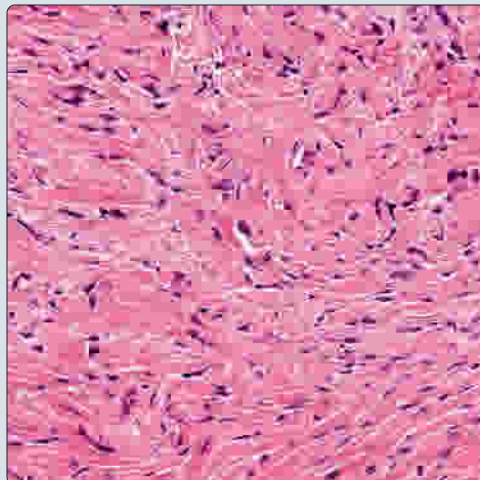


Fascicles of Spindled Cells

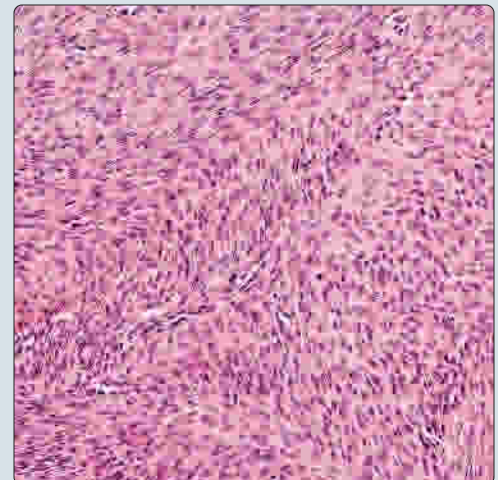


Hypocellular Fibrosarcoma

(Left) A minority of fibrosarcoma cases will show an exceedingly heavy, keloid-like collagen deposition with only a limited cellularity. In this field, there are single, isolated, atypical spindled cells. (Right) There are short, abrupt, right angle intersections to these fascicles of a fibrosarcoma. Note the elongated and tapered cells with hyperchromatic fusiform nuclei. This degree of cellularity is characteristic for a fibrosarcoma.



Herringbone Pattern



TERMINOLOGY

Synonyms

- Fibromyxosarcoma

Definitions

- Malignant neoplasm with only fibroblastic &/or myofibroblastic differentiation
 - Tumors must lack additional histologic or immunophenotypic differentiation features
 - Pleomorphic, bizarre cells move tumor into pleomorphic sarcoma category

ETIOLOGY/PATHOGENESIS

Etiology

- Isolated patients with documented radiation exposure

Pathogenesis

- (Myo)fibroblast is considered progenitor cell

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon sinonasal tract tumor
 - 2nd most common sinonasal tract nonepithelial malignancy (lymphoma is 1st)
 - ~ 3% of sinonasal **malignancies**
 - ~ 5% of all nonepithelial sinonasal tract **lesions**
- Age
 - Peak: 5th to 6th decades
- Sex
 - Female > male (3:2)

Site

- 1 or more paranasal sinuses (maxillary, ethmoid)
 - Nasal cavity alone is much less common
- Infantile-type fibrosarcoma: Develops near choana

Presentation

- Nasal obstruction and epistaxis most common
- Pain, sinusitis, nasal discharge, swelling less common
- Symptoms usually of short duration
- Anosmia and proptosis very rare
- Isolated case reports of fibrosarcoma developing as malignant transformation from nasopharyngeal angiofibroma

Treatment

- Options, risks, complications
 - Initial biopsy to confirm diagnosis before radical resection
- Surgical approaches
 - En bloc resection yields best long-term outcome
- Radiation
 - Adjuvant radiation after surgical extirpation

Prognosis

- Generally good, with 75% 5-year survival
 - Better prognosis for low-grade tumors (majority of patients have low-grade tumors)

- May result in death due to local infiltration or by distant metastasis
 - Recurrences are high (up to 60%), especially in incompletely excised tumors
 - Recurrences precede distant metastases
 - Distant metastases in ~ 15%: Lung and bones most common (rarely lymph nodes)
- Poor prognosis associated with
 - Males, large tumors, tumor stage, high-grade tumors (including high mitotic index, high cellularity), incompletely excised tumors (positive margins)

IMAGING

Radiographic Findings

- Aggressive, poorly marginated soft tissue mass with bone destruction and fascial plane destruction
- Best study: Thin-section bone CT combined with T1WI MR with contrast

MR Findings

- T1WI: Iso- to hypointense mass, often heterogeneous
- T2WI: Heterogeneously hyperintense to muscle

CT Findings

- Heterogeneous soft tissue mass, possibly showing calcifications at periphery

MACROSCOPIC

General Features

- Smooth, nodular, fungating, ulcerated, fleshy mass
- Firm, homogeneous, circumscribed cut surface
- Necrosis and hemorrhage in higher grade tumors

Size

- Range: 2-8 cm

MICROSCOPIC

Histologic Features

- Unencapsulated, circumscribed, often with bone invasion
 - Calcification (**not** osteosarcoma) is seen at periphery
- Surface epithelial invagination common (~ 1/3)
 - Surface ulceration occasionally present
 - Epithelial entrapment must not be mistaken for part of tumor (inverted papilloma, synovial sarcoma)
- Cellularity is variable but usually high
- Spindled tumor cells arranged in short, compact fascicles at acute angles
 - Herringbone or chevron pattern
 - Storiform pattern is usually absent
 - Vague fasciculated pattern can be seen
- Fusiform cells with centrally placed, hyperchromatic, needle-like nuclei with tapering cytoplasm
 - Mild pleomorphism, small nucleoli, clumped heterochromatin
 - Syncytial appearance is common
- Mitotic figures: Low in low-grade tumors
 - Increased to high in high-grade tumors
- Bizarre, pleomorphic cells are usually absent
- Stroma shows vascularity with delicate collagen fibrils to dense, keloid-like deposition

- Myxoid and edematous change can be seen
- **Low grade:** Vast majority of tumor; moderate cellularity, limited pleomorphism, few mitoses, no necrosis
- **High grade:** Nuclear pleomorphism, high mitotic activity, scant collagenous stroma, necrosis, and hemorrhage

Margins

- Must be clear to decrease chance of recurrence
- Difficult to assess, especially at intraoperative frozen section

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** Strong, diffuse cytoplasmic vimentin
 - Rarely, weak, focal actin

DIFFERENTIAL DIAGNOSIS

Fibromatosis (Desmoid Type)

- Mature fibroblasts without atypia in rich collagenous matrix
- Positive nuclear reaction with β -catenin

Solitary Fibrous Tumor

- Plump fibroblasts in mature collagenous stroma, sometimes with vessels, lacking mitoses
- Strong, diffuse CD34, Bcl-2, and vimentin reactions

Synovial Sarcoma

- Spindled cell tumor but shows epithelial differentiation
- Epithelial markers and TLE1 (nuclear) are helpful
- Characteristic t(X;18)(p11.2;q11.2) (*SSX1*, *SSX2*, or *SSX4* and *SS18*)

Spindle Cell Squamous Cell Carcinoma

- Epithelial malignancy, often showing surface connection (with ulceration)
- Spindled &/or epithelioid morphology
- Epithelial immunohistochemistry (including pancytokeratin, p63, and CK5/6), although absent in up to 30%

Melanoma (Spindle Cell Type)

- May show surface origin, but usually has necrosis, increased mitoses, and peritheliomatous growth
- **Positive:** S100 protein, SOX10, HMB-45, Melan-A, tyrosinase

Malignant Peripheral Nerve Sheath Tumor (MPNST)

- Low- and high-grade tumors show variable S100 protein staining
- Malignant triton tumor is MPNST with S100 protein staining and rhabdomyoblastic differentiation

Biphenotypic Sinonasal Sarcoma

- Spindle cell sarcoma that often has surface epithelial islands invaginated into proliferation
- Reaction with combination of S100 protein **and** actins would be different from fibrosarcoma (which may show actins in some cases)

Teratocarcinosarcoma

- Composite tumor showing fibrosarcoma, carcinoma (squamous or adenocarcinoma), and primitive neuroectodermal elements

Undifferentiated Pleomorphic Sarcoma

- Usually has profound pleomorphism, high-grade nuclear appearance, high mitotic index, and necrosis
- By definition should only have vimentin positive

Rhabdomyosarcoma

- High-grade tumor frequently with mitoses, necrosis, and invasion
- When spindled cell population, seek eccentric eosinophilic cytoplasm and possible strap cells
- Muscle markers positive (including myogenin, MYOD1, myoglobin)

Glomangiopericytoma

- Patternless proliferation below intact surface with well-developed peritheliomatous hyalinization, patulous vessels, along with eosinophils and mast cells, extravasated erythrocytes
- **Positive:** Nuclear reaction with β -catenin; actins

Inflammatory Myofibroblastic Tumor

- Extensive inflammation, haphazard distribution, of spindled cells
- May have ganglion-type cells
- Often ALK(+)

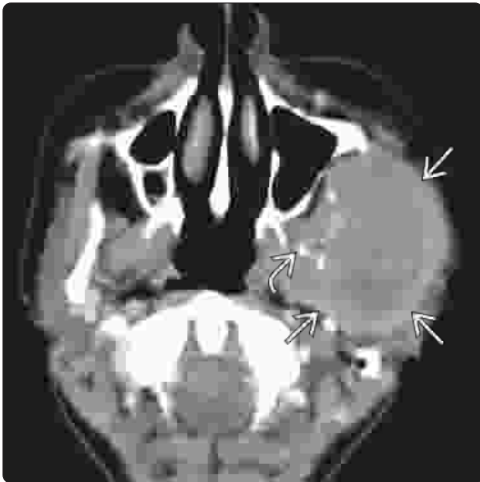
Infantile Myofibroma

- Mixed tumor with spindle cell population combined with small round blue cell elements
 - May need several levels/deepers to see primitive cells
- Rare in nasal cavity (much more common in orbit)

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CT: Large Masticator Space Mass

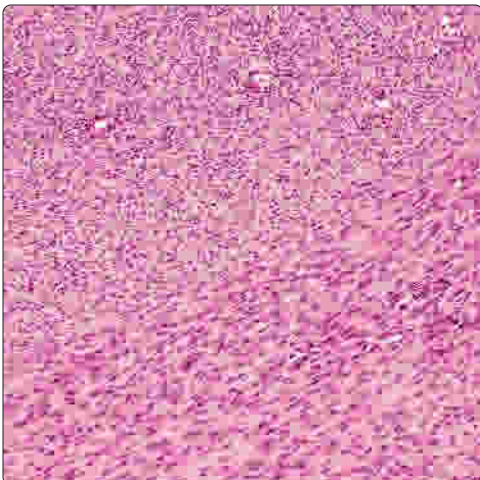


Acute Angle Intersection

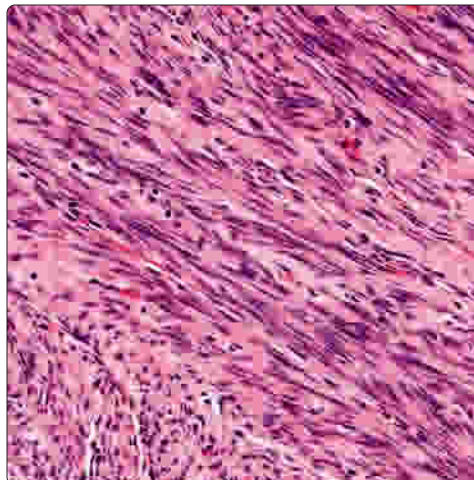


(Left) CECT shows a large heterogeneous, centrally necrotic mass with scattered coarse calcifications in the masticator space. The lesion destroys the mandible, medial and lateral pterygoid, temporalis and masseter muscles. Bone destruction is present. (Right) This low-power view of a fibrosarcoma shows acute angle intersection of fascicles of spindled cells. Fibrosarcomas are usually quite cellular tumors, although there is usually a lack of significant pleomorphism.

Limited Pleomorphism

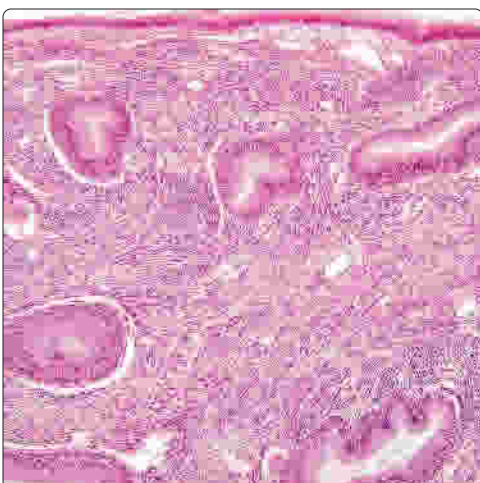


Fusiform Neoplastic Cells

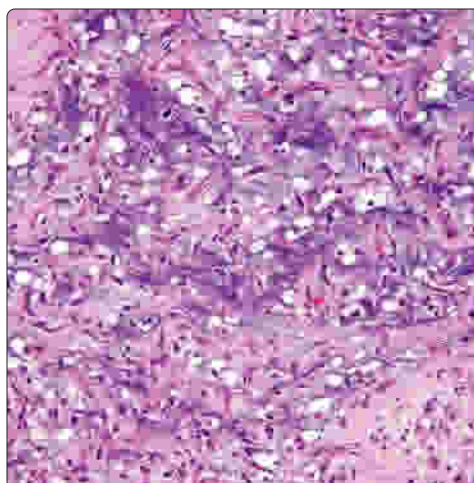


(Left) There are 2 fascicles in this image that show a neoplastic spindled cell population with limited pleomorphism. There is no necrosis and no increased mitoses. (Right) Fusiform cells are arranged in a compact fascicle. The syncytial cells show centrally placed, hyperchromatic, needle-like nuclei with tapering cytoplasm. There is limited to absent pleomorphism.

Entrapped Surface Epithelium



Myxoid Stroma



(Left) H&E shows surface epithelial invagination. The entrapment of the epithelium may mimic an inverted papilloma, respiratory epithelial adenomatoid hamartoma, synovial sarcoma, or low-grade sarcoma with neural and myogenic features. (Right) A fibromyxosarcoma has a myxoid stroma in the background of the neoplastic proliferation. In this tumor type, it is not uncommon for the short, compact fascicle pattern to be lost. There can be slight atypia; however, there is usually not profound nuclear pleomorphism.

Leiomyosarcoma

KEY FACTS

TERMINOLOGY

- Leiomyosarcoma (LMS): Malignant tumor of smooth muscle

ETIOLOGY/PATHOGENESIS

- Appears to arise from vascular structures
- May develop following irradiation or cyclophosphamide exposure
- Link between LMS and Epstein-Barr virus (EBV) identified (referred to as EBV-associated smooth muscle tumors)
 - Greater frequency of occurrence in immunocompromised patient
 - Tendency to occur in children, to occur in relationship to viscera; may be multifocal, may disseminate and be lethal

CLINICAL ISSUES

- ~ 4% arise in head and neck
- Occurs in wide age range; most common in 6th decade
- Most common sites in head & neck include oral cavity and sinonasal tract

- Complete surgical excision is treatment of choice
- Prognosis is dependent on site and extent of tumor
 - Nasal cavity: Good prognosis; cured following complete excision
 - Both nasal cavity and paranasal sinuses: Aggressive neoplasm associated with increased recurrence and mortality rates


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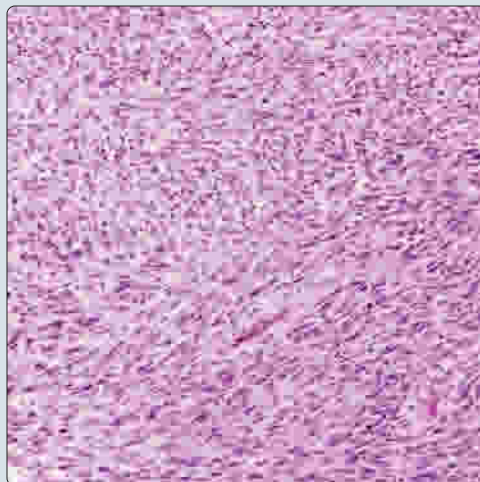
- Interlacing fascicular to storiform bundles of spindle-shaped cells typically intersect at right angles
- Elongated (spindle) cells with centrally located, blunt-ended, cigar-shaped nuclei and eosinophilic cytoplasm
- Variable degree of nuclear pleomorphism and hyperchromasia and increased mitotic activity

ANCILLARY TESTS

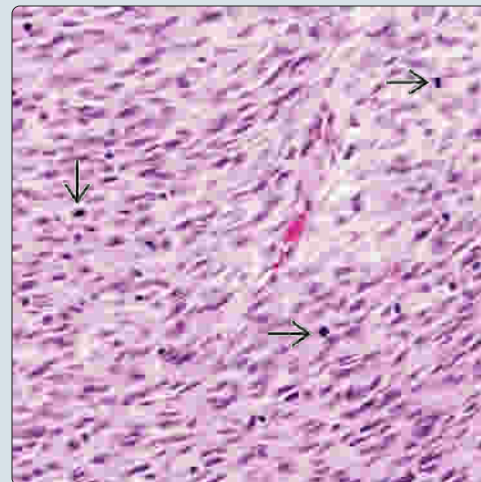
- Actins (smooth muscle and muscle specific), desmin, and caldesmon positive

Fascicular Growth

(Left) Sinonasal submucosal cellular infiltrate shows fascicular growth composed of interlacing bundles of neoplastic cells intersecting at right angles. This overall appearance suggests a possible diagnosis of a smooth muscle neoplasm. (Right) Sinonasal spindle-shaped cellular proliferation is shown with nuclear pleomorphism and increased mitotic activity . The overall mitotic count was ≥ 4 mitoses per 10 HPFs.

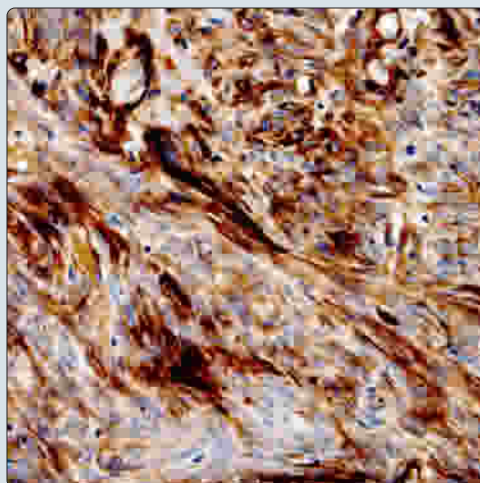


Nuclear Pleomorphism and Mitoses

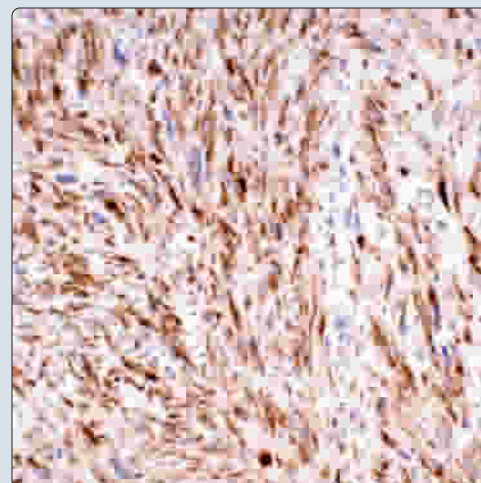


Smooth Muscle Actin Expression

(Left) The presence of smooth muscle actin staining, a consistent finding, supports the light microscopic features in leiomyosarcoma (LMS). As head and neck LMS is rare, differentiation is required from other spindle cell neoplasms. (Right) In addition to smooth muscle and muscle specific actin, leiomyosarcomas are often immunoreactive for desmin, which may be present in 70-80% of cases. Caldesmon staining (not shown) may be present in as high as 65% of cases.



Desmin Expression



TERMINOLOGY

Definitions

- Malignant tumor of smooth muscle

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- May develop following irradiation or cyclophosphamide exposure

Infectious Agents

- Link between LMS and Epstein-Barr virus (EBV) identified (referred to as EBV-associated smooth muscle tumors)
 - Greater frequency of occurrence of leiomyosarcomas (in general not necessarily those of head and neck) in immunocompromised patients, including post-transplantation (e.g., renal, cardiac, liver), AIDS
 - Tendency to occur in children, to occur in relationship to viscera (e.g., gastrointestinal tract, lung, other); may be multifocal, may disseminate and be lethal
 - EBV found by immunohistochemistry, in situ hybridization, &/or PCR

Histogenesis

- Appears to arise from vascular structures
 - Due to relative lack of smooth muscle in head and neck region
 - Other than relationship to vascular walls, histology similar to nonvascular-derived LMS

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~ 4% arise in head and neck
- Age
 - **Nonimmunocompromise-associated LMS**
 - Occurs in wide age range
 - Most common in 6th decade
 - **Immunocompromise-associated LMS**
 - Tends to occur in children or young adults
- Sex
 - Equal gender distribution

Site

- **Nonimmunocompromise-associated LMS**
 - Most common sites
 - Oral cavity (buccal mucosa, gingiva, tongue, floor of mouth), sinonasal tract
 - Skin and subcutaneous tissue
 - Less common sites
 - Larynx, trachea, neck, hypopharynx, orbit, external auditory canal
- **Immunocompromise-associated LMS**
 - Tend to occur in relationship to viscera (e.g., gastrointestinal tract, lung)
 - May be multifocal

Presentation

- Nasal obstruction, pain, epistaxis, painless mass

Treatment

- Surgical approaches
 - Complete surgical excision is treatment of choice
- Radiation and chemotherapy are of questionable utility

Prognosis

- Dependent on site and extent of tumor
- Not necessarily contingent on histology
 - Nasal cavity
 - Good prognosis
 - Cured following complete removal
 - Both nasal cavity and paranasal sinuses
 - Aggressive neoplasm associated with increased recurrence (70% of patients)
 - Increased mortality rates (45% of patients with death occurring within 2 years of diagnosis)
- Local recurrence frequent
 - Usually associated with extensive, uncontrollable local infiltration
- Metastases (hematogenous) infrequent early but can occur late in disease course
- EBV-associated smooth muscle tumors may disseminate and be lethal

IMAGING

General Features

- Soft tissue density, sinus opacification, bone erosion &/or invasion

MACROSCOPIC

General Features

- Circumscribed but not encapsulated, tan-white to pink-red, rubbery to firm, polypoid or sessile lesion
- Ulceration, hemorrhage, necrosis, and invasion of adjacent structures often identifiable

Size

- Usually > 5 cm in diameter

MICROSCOPIC

Histologic Features

- Interlacing fascicular to storiform bundles of spindle-shaped cells
 - Typically intersect at right angles
- Neoplastic cells are elongated (spindle) with centrally located, blunt-ended, cigar-shaped nuclei and eosinophilic cytoplasm
 - Perinuclear vacuole or clear halo may be seen, giving nucleus indented or concave contour
- Variable degree of cellular anaplasia with nuclear pleomorphism, nuclear hyperchromasia, and increased mitotic activity (typical and atypical forms)
 - Marked nuclear pleomorphism may be present
- Nuclear palisading may be prominent
 - May suggest diagnosis of peripheral nerve sheath tumor
- Other cell types
 - Multinucleated giant cells commonly seen
 - Epithelioid cells may predominate, conferring designation of epithelioid LMS

Leiomyosarcoma

- Stroma tends to be richly vascular with close apposition of tumor to vascular structures
 - Myxomatous stromal changes may be prominent, conferring designation of myxoid LMS
- Infiltrative
 - Usually indicative of malignancy
 - Limited infiltrative growth can be seen in smooth muscle tumors of uncertain malignant potential

Myxoid LMS

- Extensive myxoid change may create gelatinous appearance
- Prominent myxoid stroma rich in hyaluronic acid is present between spindled neoplastic cells
- Overall appearance relatively hypocellular
 - In presence of low mitotic rate, overall histology may not be suggestive of malignant neoplasm
- Even mitotic rates ≤ 2 mitotic figures should prompt consideration for malignancy

Inflammatory Leiomyosarcoma

- Characterized by presence of prominent inflammatory cell infiltrate
 - Including xanthoma cells, lymphocytes, and occasionally neutrophils
 - Not associated with systemic (constitutional) symptoms

Epithelioid LMS

- Predominantly composed of epithelioid cells with round to oval nuclei
 - Transitional areas from epithelioid to spindle-shaped areas
 - Clear or vacuolated-appearing cytoplasm may be prominent

Granular Cell LMS

- Rare variant characterized by cells with granular eosinophilic cytoplasm

Criteria for Malignancy

- Tumors with 1-4 mitoses per 10 HPF considered potentially malignant
 - Especially in conjunction with nuclear atypia and necrosis
- > 4 mitoses per 10 HPF is malignant
- If tumors have no/very few mitoses and absence of nuclear atypia, then tumor is likely benign
 - Even in presence of increased cellularity
 - Even in presence of focal infiltrative growth
 - Especially if significant hyalinization or calcification

ANCILLARY TESTS

Histochemistry

- Masson trichrome: Cytoplasmic deep red, longitudinal lines
- PTAH: Cytoplasmic purple appearing
- Glycogen demonstrable as diastase-sensitive, PAS-positive material

Immunohistochemistry

- Actins (smooth muscle and muscle specific) positive
- Desmin reactivity (70-80%) present
- Caldesmon positive (60-65%)
- Usually no immunoreactivity for

- Epithelial markers (e.g., cytokeratins)
 - Cytokeratin expression may occur, usually perinuclear localization, usually seen in association with desmin reactivity
- Melanocytic markers, markers of skeletal muscle, vascular endothelial markers
 - S100 protein may be positive

DIFFERENTIAL DIAGNOSIS

Leiomyoma

- Even if cellular, lacks significant pleomorphism and mitotic activity

Smooth Muscle Tumor of Uncertain Malignant Potential

- Shows moderate nuclear pleomorphism but not more than 4 mitoses per 10 HPF

Spindle Cell Squamous Carcinoma

- Presence of squamous cell carcinoma (i.e., dysplasia, invasive differentiated carcinoma)
- Immunoreactivity for epithelial markers (cytokeratins, p63) seen in majority of cases

Malignant Peripheral Nerve Sheath Tumor (MPNST)

- Overlapping features but typically only S100 protein immunoreactive, lacking actin staining

Biphenotypic Sinonasal Sarcoma

- Low-grade sinonasal sarcoma with concurrent neural and myogenic differentiation

Fibrosarcoma/Undifferentiated Pleomorphic Sarcoma

- Diagnosis of exclusion lacking immunoreactivity associated with LMS

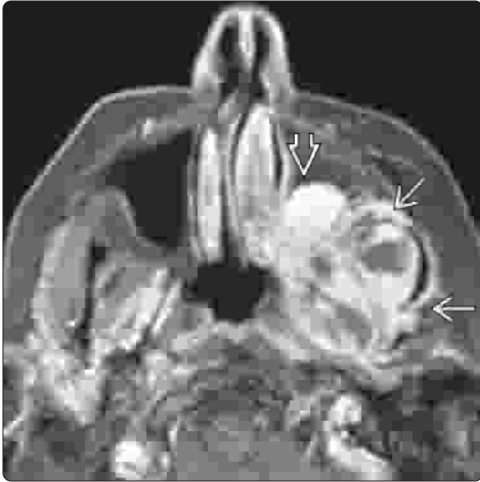
Rhabdomyosarcoma

- Consistent immunoreactivity for markers of skeletal muscle differentiation including
 - Desmin, muscle specific actin, myoglobin, MYOD1, myogenin

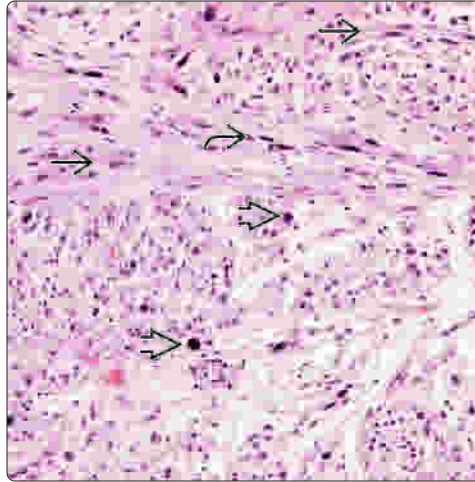
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Leiomyosarcoma, High Grade, Imaging Findings

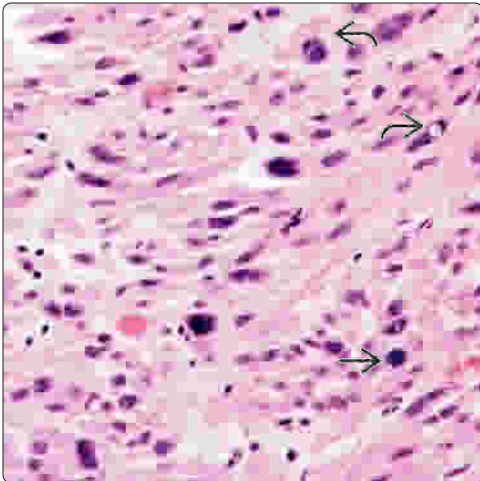


High-Grade Nuclear Morphology

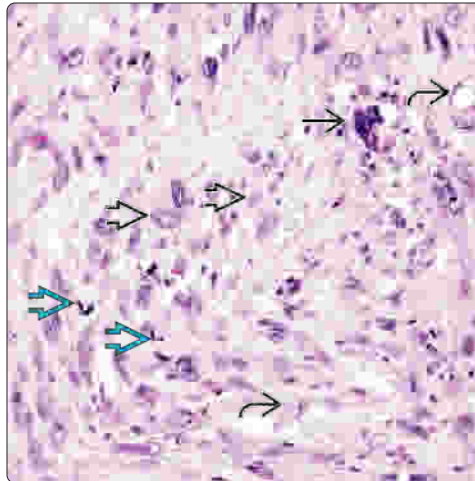


(Left) Axial T1 C+ MR with fat suppression shows left maxillary space leiomyosarcoma with left maxillary sinus invasion. Marked inhomogeneous enhancement suggests a high-grade lesion. (Right) LMS is shown with interlacing bundles of spindle-shaped cells, intersecting at right angles associated myxoid stroma. The neoplastic cells are elongated with blunt-ended nuclei, eosinophilic cytoplasm, and occasional perinuclear vacuoles and mitotic figures.

Marked Nuclear Pleomorphism

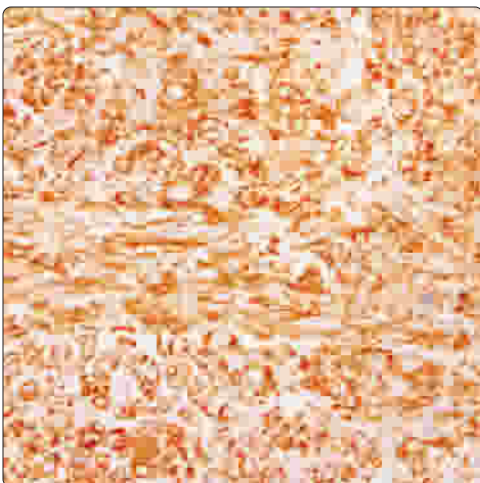


Atypical Mitoses

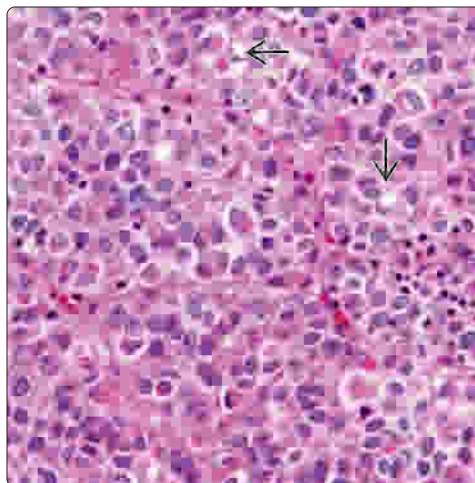


(Left) LMS is characterized by spindle-shaped cells with marked nuclear pleomorphism and hyperchromasia, cytoplasmic vacuoles, and increased mitotic activity. (Right) LMS shows markedly pleomorphic nuclei including a multinucleated cell, eosinophilic intranuclear inclusions, vacuolated cells, and increased mitotic activity, including atypical forms. These histologic features suggest a tumor of possible smooth muscle origin but require immunohistochemical staining for diagnosis.

Smooth Muscle Actin Expression



Epithelioid Cell Morphology



(Left) Smooth muscle actin immunoreactivity with absence of reactivity for other markers (e.g., epithelial, melanocytic, other sarcomas) that may indicate an alternative diagnosis is confirmatory for LMS. (Right) Epithelioid LMS is composed of epithelioid cells, characterized by round to oval nuclei, and eosinophilic to clear/vacuolated-appearing cytoplasm. There were foci transitioning from more characteristic spindled-shaped cells, and smooth muscle actin staining (not shown).

Malignant Peripheral Nerve Sheath Tumor

KEY FACTS

TERMINOLOGY

- Malignant neoplasm (sarcoma) arising from cells intrinsic to nerve sheath or having differentiation along lines of various elements of nerve sheath

CLINICAL ISSUES

- Uncommon tumor accounting for ~ 5% of all soft tissue sarcomas
 - Most commonly occurs in lower extremity
 - Up to 20% may occur in head and neck with neck most common site
 - Other sites of involvement include sinonasal tract, nasopharynx, oral cavity
- Complete surgical excision (gross total resection) is treatment of choice
- Owing to prevalence of higher grade lesions, overall 5-year survival rate ~ 30-60%

MICROSCOPIC

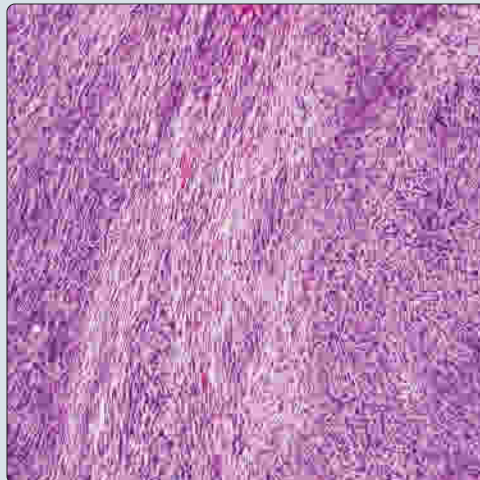
- Most MPNSTs are high grade
 - Unencapsulated hypercellular proliferation composed of spindle-shaped cells
 - Cells arranged in fascicular growth with long sweeping (herringbone-like) fascicles that swirl or interdigitate with one another
 - Nuclei tend to be hyperchromatic and pleomorphic with inconspicuous nucleoli
 - Mitoses generally readily identifiable; necrosis can be found

ANCILLARY TESTS

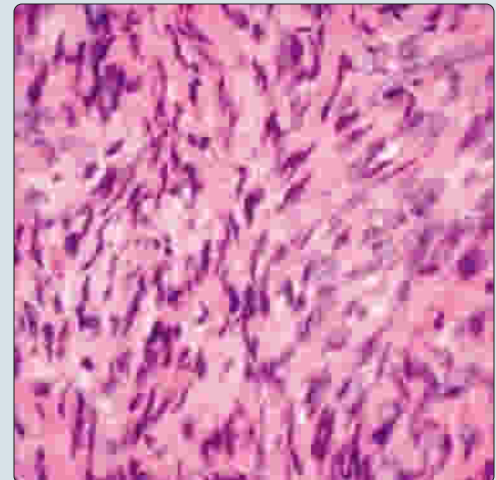
- In high-grade tumors, S100 protein may be focally positive or even negative
- SOX10 (nuclear staining) reported to show better sensitivity and specificity in the diagnosis of MPNST than S100 protein

Fascicular Growth

(Left) High-grade MPNST is characterized by the presence of fascicular to storiform growth and increased cellularity. The degree of cellularity (as well as nuclear pleomorphism and mitotic activity) is significantly greater than the findings seen in benign schwannomas and low-grade MPNSTs. **(Right)** At high magnification, the lesional cells of high-grade MPNST include wavy or buckled nuclei suggesting a neurogenic neoplasm with hyperchromasia and nuclear pleomorphism.

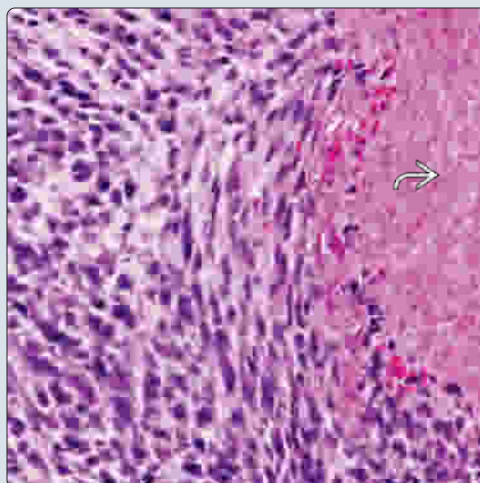


Wavy-Appearing Nuclei

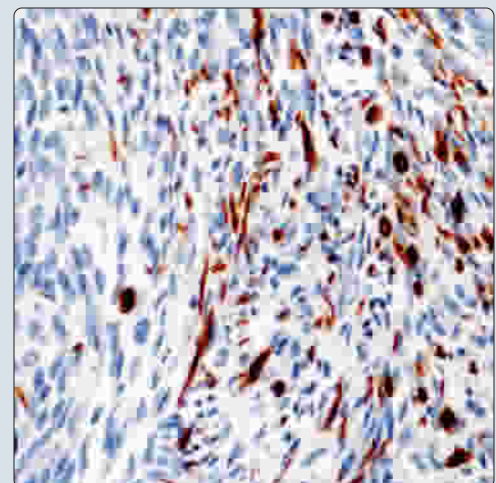


Confluent Tumor Necrosis

(Left) High-grade MPNST shows increased cellularity, nuclear pleomorphism, and necrosis. Although not illustrated here, there was also an increase in mitotic activity. **(Right)** S100 protein staining, in the absence of any other specific immunostaining that is diagnostic for an alternative neoplasm, supports the diagnosis of a high-grade MPNST; however, in contrast to schwannomas and low-grade MPNST, S100 protein staining in high-grade MPNST is often only focally identified.



Focal S100 Protein Expression



TERMINOLOGY

Abbreviations

- Malignant peripheral nerve sheath tumor (MPNST)

Synonyms

- Malignant schwannoma, neurogenic sarcoma, neurofibrosarcoma

Definitions

- Malignant neoplasm (sarcoma) arising from cells intrinsic to nerve sheath or having differentiation along lines of various elements of nerve sheath

ETIOLOGY/PATHOGENESIS

Neurofibromatosis (NF)

- Occurs in setting of NF1
 - Accounts for ~ 30-50% of all MPNSTs
 - Lifetime risk in patients with NF1 is 5-10%
 - Estimated risk of patients with NF1 developing MPNST varies (4-50%)
 - Occurrence typically follows latent period of 10-20 years
 - MPNST not associated in patients with NF2
 - Rare example of MPNST spontaneously developing in patient with NF2 reported
 - Rarity of development of MPNST in NF2 patients may be attributed to resistance of nonmelanotic schwannomas (which occur in NF2) to malignant transformation

Idiopathic

- De novo (sporadic) MPNST

Post Irradiation

- Infrequently may occur in areas previously irradiated
- ~ 10% are radiation-induced with posttreatment latency period usually > 10 years

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon tumor accounting for ~ 5% of all soft tissue sarcomas
 - Most commonly occurs in lower extremity
 - Up to 20% may occur in head and neck
- Age
 - **De novo MPNST**
 - Occurs over wide age range, but most frequently in 5th decade
 - **MPNST associated with NF1**
 - Primarily seen in 3rd-4th decades of life; can also occur in children
- Sex
 - **De novo MPNST**
 - No gender predilection or slightly more common in females
 - **MPNST associated with NF1**
 - No gender predilection or slightly more common in females

Site

- Most common site of involvement is neck
 - Less frequently, other sites of involvement include sinonasal tract, nasopharynx, oral cavity

Presentation

- Neck symptoms include
 - Mass with associated pain, paresthesia, weakness
- Sinonasal tract, nasopharynx, oral cavity symptoms include
 - Mass lesion, pain, epistaxis, and nasal obstruction

Treatment

- Surgical approaches
 - Complete surgical excision (gross total resection) is treatment of choice
 - Most MPNSTs are high-grade malignancies necessitating wide en bloc resection and postoperative radiotherapy
- Adjuvant therapy
 - Chemotherapy utilized for inoperable tumors and disseminated tumors

Prognosis

- Owing to prevalence of higher grade lesions, overall 5-year survival rate ~ 30-60%
- Survival of patients with NF1-associated MPNST previously believed to be lower than in patients with sporadic MPNST, but controversial issue and likely not valid
- Local recurrence is common, reported in up to 50% of patients
- Regional nodal metastases are uncommon (10% or less of patients) and as result nodal neck dissection is generally not warranted
- Distant metastases occur in ~ 33% of cases and most commonly spread to lungs; less common metastatic sites include bone, pleura, and liver
- Additional adverse prognostic findings include
 - Larger tumor size (> 5 cm)
 - Resection with positive margin and (local) recurrence
 - Distant metastasis: Increased risk of distant metastasis in large tumor, AJCC stage III, lack of S100 protein staining and in patient requiring chemotherapy
 - Radiation-induced sarcoma
 - Malignant Triton tumors are particularly aggressive

MACROSCOPIC

General Features

- Fusiform-shaped mass with fleshy, tan-white appearance
- Attachment to nerve may be identified

Size

- Usually > 5 cm in diameter

MICROSCOPIC

Histologic Features

- Most MPNSTs are high-grade and the following reflects those high-grade lesions
- Unencapsulated hypercellular proliferation composed of spindle-shaped cells

Malignant Peripheral Nerve Sheath Tumor

- Cells arranged in fascicular growth with long sweeping (herringbone-like) fascicles that swirl or interdigitate with one another
 - Less common growth patterns may include nodules or whorled arrangement of neoplastic cells
 - In ~ 10% of cases, abundant myxoid stroma may be present (myxoid MPNST)
- Cells have elongated nuclei with irregular contour, tapered ends
 - Nuclei appear wavy or buckled in profile and asymmetrically oval en face with indistinct cytoplasm
- Nuclear palisading may be seen
 - Typically is present in minority of cases (< 10%)
- Nuclei tend to be hyperchromatic and pleomorphic with inconspicuous nucleoli
- Mitoses generally readily identifiable
 - Most cases show at least 4 mitotic figures per 10 HPF; mitotic counts of 10-20 per 10 HPF are common
- Necrosis can be found, including geographic type; with tendency to spare lesional cells surrounding blood vessels (peritheliomatous pattern)
- Heterologous elements can be identified in up to 15% of cases
 - Most common elements include mature cartilage and bone
 - Tend to be more commonly seen in association with MPNST than other sarcomas

Low-Grade MPNST

- Minority of cases are low-grade, and distinction from benign nerve sheath tumor with atypical features can be problematic
- As compared to benign nerve sheath tumors, low-grade MPNSTs have
 - Increased cellularity and increased mitotic activity; mitoses may be few in number but atypical mitoses are not typically present
 - May demonstrate infiltrative growth
 - Necrosis is usually not present

Histologic Variants

- MPNST with rhabdomyosarcoma (malignant Triton tumor)
- MPNST with glands (glandular malignant schwannoma)
- Epithelioid MPNST
- MPNST with perineurial differentiation (perineurial cell MPNST)

ANCILLARY TESTS

Immunohistochemistry

- S100 protein reactivity seen in 50-90% of tumors with extent and intensity of reactivity dependent on grade of tumor
 - **High-grade MPNST**
 - S100 protein may be focally positive with even less immunoreactivity than low-grade tumors
 - May be S100 protein negative
 - **Low-grade MPNST**
 - S100 protein positivity present but, in contrast to schwannoma and neurofibroma, is less diffusely/intensely positive

- SOX10 (nuclear staining) reported to show better sensitivity and specificity in the diagnosis of MPNST than S100 protein
- Other markers that may be positive include GFAP (20-30%); variable CD57; p53 expression (nuclear) present in high proportion of cases

Genetic Testing

- No consistent karyotypic pattern
 - Complex and nonspecific karyotype abnormalities including chromosomal gains and losses
 - Often show *NF1* gene deletion or mutation: Patients with NF1 carry germline alterations in *NF1* gene

DIFFERENTIAL DIAGNOSIS

Synovial Sarcoma (SS)

- Shares overlapping histologic features with MPNST
 - SS immunoreactive for epithelial markers (EMA, CK7, CK19), S100 protein (30%), CD99, TLE1
 - Presence of *SS18* (*SYT*) gene rearrangement

Fibrosarcoma

- More uniform fascicular growth pattern
- Cells resemble fibroblasts with symmetric fusiform appearance
- Absence of neural differentiation

Leiomyosarcoma (LMS)

- Overlapping features with MPNST; some distinguishing features include
 - Presence of blunt-ended, cigar-shaped nuclei, juxtanuclear vacuoles
 - Presence of myogenic markers (actins, desmin, caldesmon)

Biphenotypic Sinonasal Sarcoma

- Low-grade sinonasal sarcoma with concomitant neural and myogenic differentiation

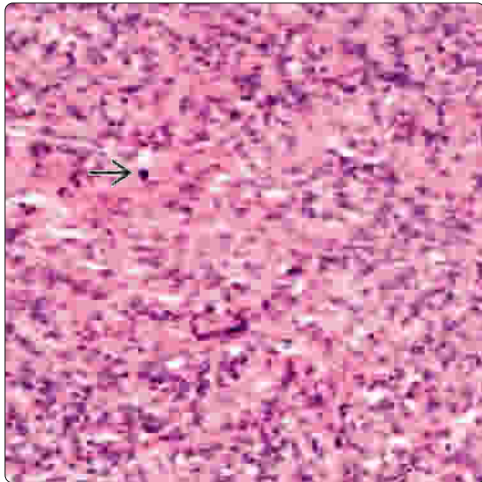
Malignant Melanoma

- Distinguished on basis of immunohistochemical findings
 - Melanomas reactive for melanocytic markers, including HMB-45, Melan-A, tyrosinase

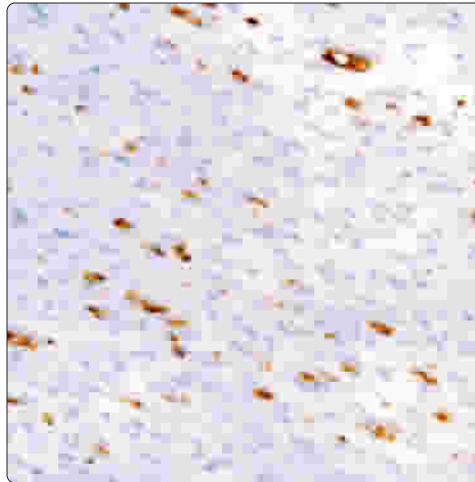
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Nuclear Pleomorphism and Mitoses

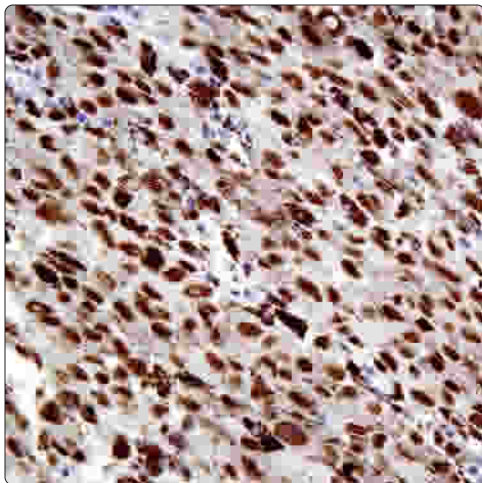


Focal S100 Protein Expression

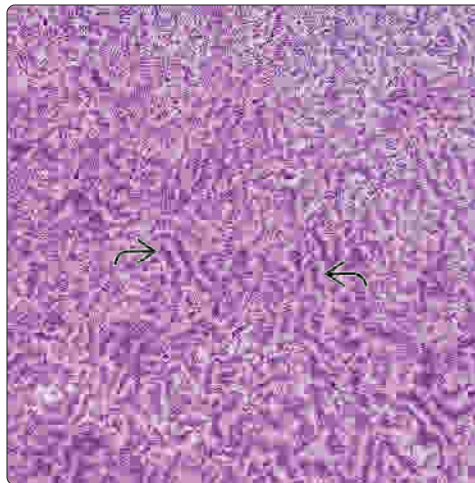


(Left) Cellular lesion with nuclear pleomorphism and increased mitotic figures [1] is shown. The overall features are not diagnostic for a neurogenic neoplasm and could represent any high-grade malignant neoplasm. Transitional areas from foci more diagnostic of a peripheral nerve sheath tumor (not shown), as well as focal S100 protein staining, support the diagnosis. **(Right)** S100 protein immunoreactivity in high-grade MPNST tends to be limited in extent but assists in supporting the diagnosis.

SOX10 Expression

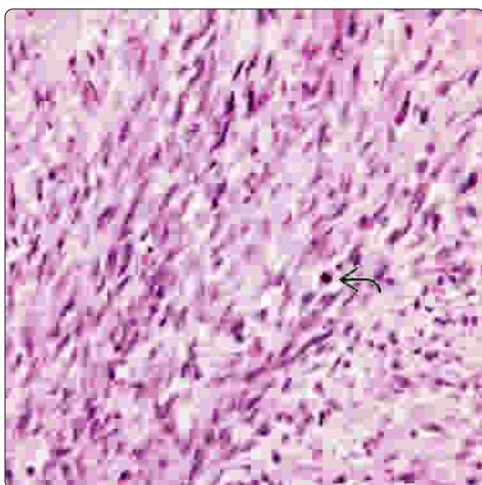


Nuclear Palisading

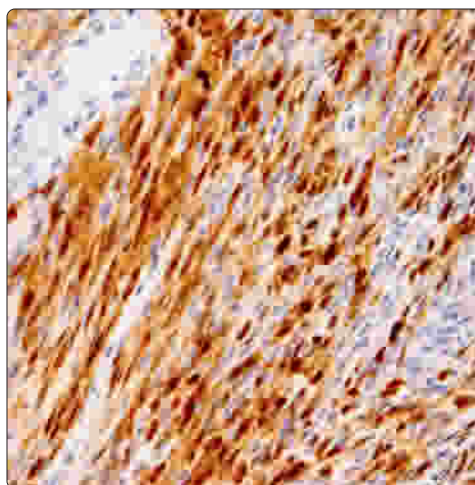


(Left) Diffuse and strong nuclear staining for SOX10 represents another marker that can be used in MPNSTs reported to have greater sensitivity and specificity in the diagnosis of MPNST than S100 protein. **(Right)** Nuclear palisading with parallel arrangement of the neoplastic cells [2] is a feature that can be seen in both benign and malignant peripheral nerve sheath tumors (and in other tumor types). In addition to the nuclear palisading, MPNSTs show nuclear atypia, increased mitotic activity, and may have infiltrative growth.

Increased Cellularity and Mitoses



Diffuse S100 Protein Expression



(Left) Low-grade MPNST shows fascicular growth with buckled or wavy-appearing nuclei. As compared to benign schwannomas, there is increased cellularity with nuclear pleomorphism and increased mitotic activity [3]. **(Right)** In low-grade MPNSTs, S100 protein staining tends to be diffuse and strong, similar to that in benign schwannomas but much greater than in high-grade MPNSTs. Differentiation from benign schwannomas is based on cellularity, atypia, mitotic activity, and infiltrative growth.

Undifferentiated Pleomorphic Sarcoma

KEY FACTS

TERMINOLOGY

- High-grade, pleomorphic malignant neoplasm without specific differentiation and not associated with differentiated sarcoma
 - Diagnosis is one of excluding another more specific sarcoma or nonsarcomatous neoplasm
- Undifferentiated pleomorphic sarcoma is current terminology proposed by the World Health Organization used for sarcomas previously diagnosed collectively as malignant fibrous histiocytoma (MFH)

ETIOLOGY/PATHOGENESIS

- Majority occur de novo
- Represents most common post-irradiation sarcoma

CLINICAL ISSUES

- ~ 3% occur in head and neck
- Sinonasal tract most common site of occurrence
- Complete surgical excision is treatment of choice

- High recurrence and metastatic rates

MICROSCOPIC

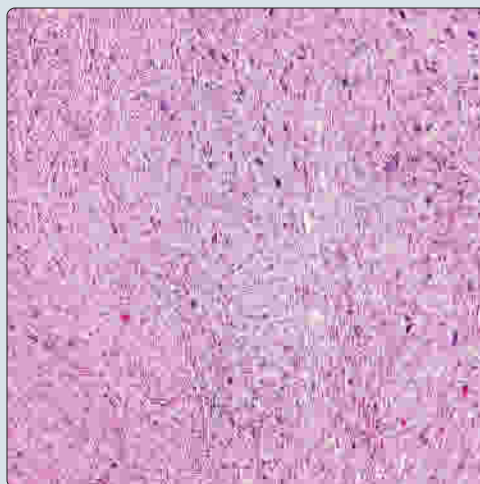
- Histologic variants include
 - Storiform-pleomorphic; myxoid; giant cell; inflammatory; angiomatoid
- Storiform-pleomorphic type most common histologic variant in sinonasal tract
 - Fascicular and storiform growth patterns
 - Marked nuclear pleomorphism, increased mitotic activity, including typical and atypical forms
 - Multinucleated giant cells
- Characteristic stromal vasculature, including capillary network arranged in curvilinear fashion seen in myxoid variant
- Heterologous elements, including bone and cartilage, may be present in any histologic subtype

ANCILLARY TESTS

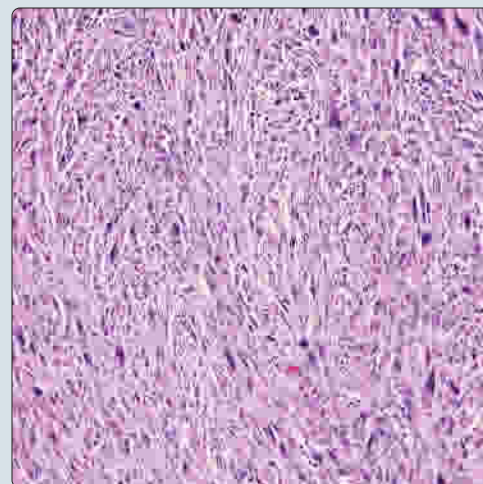
- No specific immunoreactivity

Fascicular/Storiform Pattern

(Left) Sinonasal undifferentiated pleomorphic sarcoma, pleomorphic-storiform type, shows fascicular to storiform growth patterns, a cellular proliferation that even at this magnification includes numerous multinucleated cells. (Right) Combination of spindle-shaped, epithelioid, and bizarre-appearing giant cells are identified. These overall features, while characteristic, are not pathognomonic for undifferentiated pleomorphic sarcoma, which is often a diagnosis of exclusion.

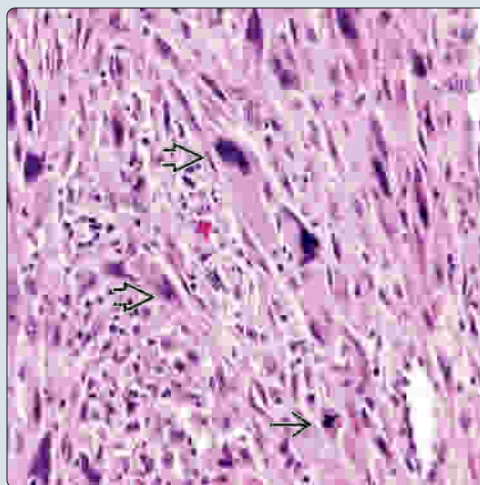


Spindle and Epithelioid Cells

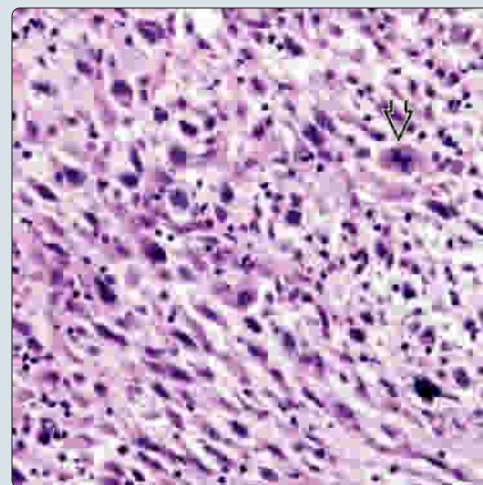


Pleomorphic Tumor Cells

(Left) Undifferentiated pleomorphic sarcoma comprised of spindle-shaped cells with marked nuclear pleomorphism, hyperchromasia [box], and increased mitotic activity, including atypical forms [box], is shown. A sparse inflammatory cell infiltrate is present. (Right) Hypercellular neoplasm consisting of spindle-shaped to epithelioid-appearing cells with marked nuclear pleomorphism, increased mitotic activity, including atypical forms [box]. A variable mixed chronic inflammatory cell infiltrate is present.



Epithelioid Tumor Cells



TERMINOLOGY

Definitions

- High-grade, pleomorphic malignant neoplasm without specific differentiation and not associated with differentiated sarcoma:
- Undifferentiated pleomorphic sarcoma is the current terminology proposed by World Health Organization used for sarcomas previously diagnosed collectively as malignant fibrous histiocytoma (MFH)
 - MFH once considered one of the more common soft tissue sarcomas of late adult life
 - With more advanced diagnostic techniques (e.g., immunohistochemistry), recognition that MFH was "wastebasket" diagnosis for lesions more accurately classified into a specific class of sarcomas (e.g., liposarcoma, others) has decreased its incidence and raised question about validity of its existence

ETIOLOGY/PATHOGENESIS

Idiopathic

- Majority occur de novo

Post Radiation

- Represents most common postirradiation sarcoma
 - In association with prior radiation latency period is usually a decade or longer from time of irradiation to development of malignancy

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon neoplasm in head and neck
 - ~ 3% occur in head and neck
- Age
 - Occurs over wide range
 - Most commonly seen in adults
- Sex
 - Male > female

Site

- Sinonasal tract most common site of occurrence
 - Maxillary sinus > ethmoid sinus and nasal cavity
 - Rare occurrence in frontal and sphenoid sinuses
- Neck 2nd most common site of occurrence
- Rare in other head and neck sites, including oral cavity, larynx

Presentation

- Mass ± associated pain, nasal obstruction, epistaxis, facial asymmetry, proptosis

Treatment

- Surgical approaches
 - Complete surgical excision is treatment of choice
 - Lymph node metastasis occurs in less than 15% of cases
 - Unless clinically suspect for nodal disease, neck dissection of limited value
- Adjuvant therapy
 - Chemotherapy used in presence of metastasis
- Radiation

- Radiotherapy may be used for tumors with positive surgical margins or close surgical margins

Prognosis

- High recurrence and metastatic rates
 - Metastases occur to the lung > lymph nodes > liver and bone
 - Death from disease is common, reported in over 75% of patients
 - Median time: 13.5 months
- Prognosis dependent on
 - Depth of tumor
 - Deep soft tissue tumors more likely to metastasize compared to tumors of subcutis
 - Size of tumor
 - Smaller tumors (less than 2.5 cm) less likely to metastasize compared to larger tumors
 - Prior radiation exposure
 - Reported 5-year disease-free survival rates of post-irradiated MFH of 0%
 - Positive margins
 - Associated with worse survival
 - Inflammatory cell component
 - Tumors with increased numbers of inflammatory cells less likely to metastasize compared to tumors lacking significant inflammatory cell infiltrate
 - Myxoid component
 - Tumors with prominent myxoid component less likely to metastasize compared to tumors lacking significant myxoid component

MACROSCOPIC

General Features

- Nodular or multinodular appearing tan-white to gray lesion
- Necrosis and hemorrhage may be apparent
- Myxoid variant appears translucent or gelatinous

MICROSCOPIC

Histologic Features

- **Storiform-pleomorphic variant**
 - Most common histologic variant in sinonasal tract
 - Fascicular and storiform growth patterns
 - Storiform growth characterized by formation of short fascicles in pinwheel or cartwheel configuration
 - Histologically high grade
 - Hypercellular neoplasm consisting of spindle-shaped to epithelioid-appearing cells
 - Marked nuclear pleomorphism, increased mitotic activity, including typical and atypical forms
 - Multinucleated &/or bizarre giant cells with multiple hyperchromatic nuclei identified
 - Necrosis commonly seen
 - Heterologous elements, including bone and cartilage, may be present
 - Granulomas may be identified
 - Variable amount of chronic inflammatory cell infiltrate that may include mature lymphocytes, plasma cells, xanthoma (foam) cells with variable numbers of neutrophils and eosinophils; granulomas may be identified

Undifferentiated Pleomorphic Sarcoma

● Myxoid variant (myxofibrosarcoma)

- Diagnosis requires that $\geq 50\%$ of tumor has myxoid stroma but prior to considering this diagnosis, myxoid variant of another defined sarcoma type must be excluded
- Tend to be multinodular characterized by cells with low nuclear grade morphology and low mitotic rate
- Cells are spindle- or stellate-shaped with hyperchromatic nuclei, limited pleomorphism, slightly eosinophilic cytoplasm, and indistinct cell borders
- Myxoid foci may be hypocellular but contain spindle-shaped and epithelioid malignant cells arranged in storiform or fascicular growth
- Cells may show features suggestive of lipoblasts, including vacuolated cytoplasm with indentation of nuclei
- Cellular foci showing features of storiform-pleomorphic type may be seen but usually are haphazardly arrayed
- Characteristic stromal vasculature, including capillary network arranged in curvilinear fashion

● Inflammatory variant

- Admixture of histiocytic-appearing cells, xanthomatous cells, and inflammatory cells, including neutrophils
- Patients may have constitutional symptoms, including fever and peripheral granulocytosis

● Giant cell variant

- Nodular or multinodular growth but also diffuse growth without nodularity
- Characterized by presence of multinucleated giant cells containing numerous (up to 100) round to oval nuclei with vesicular chromatin, identifiable nucleoli, and eosinophilic cytoplasm
 - Diagnosis requires that multinucleated giant cells and mononuclear cells represent over 50% of tumor

● Angiomatoid variant

- Soft tissue neoplasm of low malignant potential, typically occurring in superficial soft tissues of extremities in children and young adults
- Histology characterized by irregular solid masses of histiocytic-like cells, which appear uniform with round to oval nuclei and slightly eosinophilic cytoplasm
 - Nuclear atypia &/or hyperchromatic giant cells may be seen
- Cystic areas of hemorrhage are present not lined by endothelial cells
- Tendency to locally recur and rarely may metastasize

- Identification of diagnostic cells

- e.g., lipoblasts, rhabdomyoblasts

- Targeted panel of immunohistochemical stains

Spindle Cell Squamous Carcinoma

- Typically superficially located, not deep-seated
- Often associated with differentiated squamous cell carcinoma in form of
 - Intraepithelial dysplasia
 - Invasive differentiated squamous cell carcinoma
- Immunoreactivity for epithelial markers, including cytokeratins, p63
 - Significant percentage of cases may be keratin &/or p63 negative
 - Consistently vimentin reactive with variable desmin and actin immunoreactivity

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Diagnosis is one of excluding another more specific sarcoma or nonsarcomatous malignant neoplasm
 - Requires targeted panel of immunostains
 - May require molecular genetic testing

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ANCILLARY TESTS

Immunohistochemistry

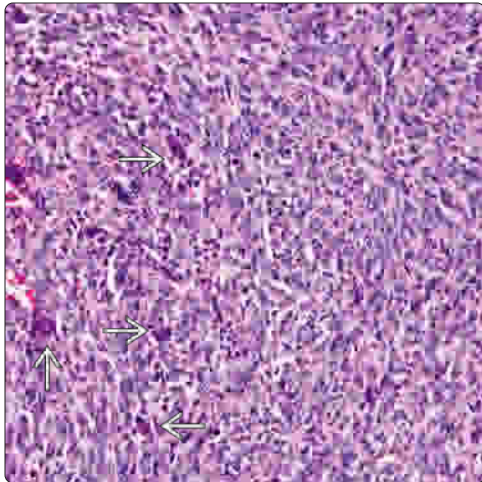
- No specific immunoreactivity
 - Vimentin (+)
 - Smooth muscle actin may be focally positive
 - Giant cells may be CD68 (+)
 - Absence of epithelial, melanocytic, myogenic and hematolymphoid markers

DIFFERENTIAL DIAGNOSIS

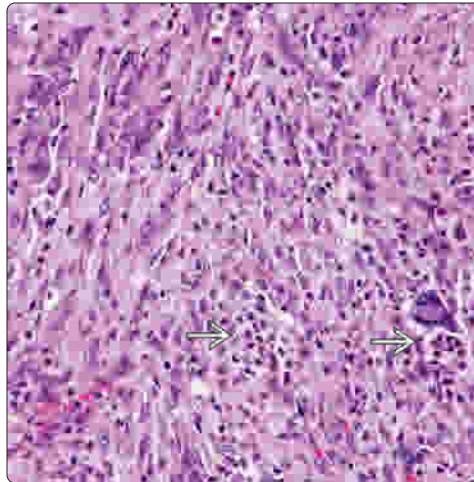
Other Pleomorphic Sarcomas

- Liposarcoma, leiomyosarcoma, rhabdomyosarcoma
- Differentiation predicated on

Undifferentiated Pleomorphic Sarcoma

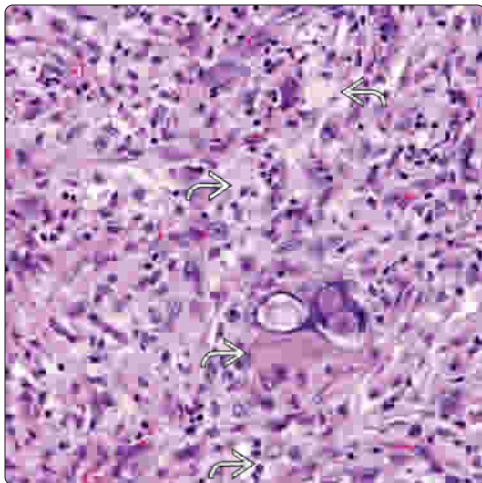


Inflammatory Cells

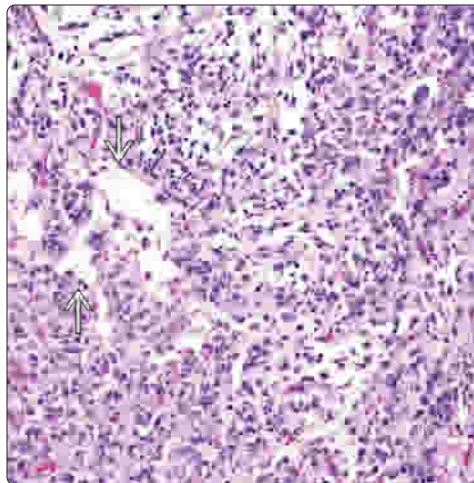


(Left) Undifferentiated pleomorphic sarcoma comprised of a dense cellular proliferation with storiform to fascicular growth, including scattered multinucleated giant cells [1], is shown here. **(Right)** A variable number of inflammatory cells are present, typically including mature lymphocytes and plasma cells, but increased numbers of neutrophils [2] may be present. Only after more common types of undifferentiated malignant neoplasms (e.g., carcinoma, other) are excluded can the diagnosis be proffered.

Increased Xanthoma Cells

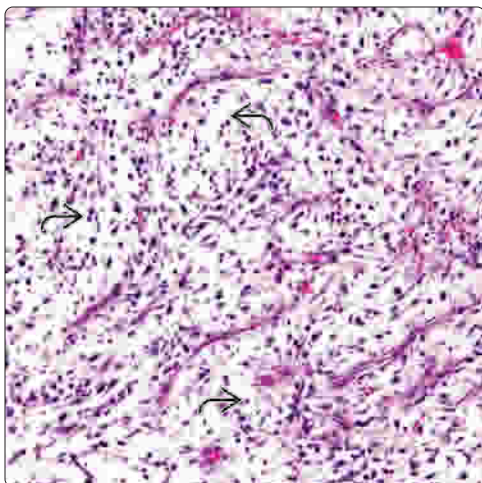


Significant Inflammatory Infiltrate

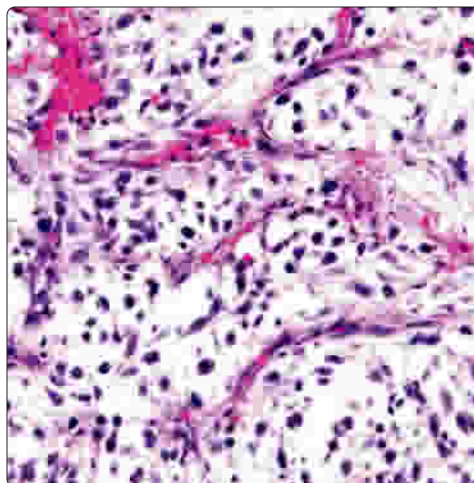


(Left) In addition to mature lymphocytes, plasma cells, eosinophils, and neutrophils, xanthoma cells [3] may represent a significant component of the inflammatory cells. Such findings, in particular the presence of xanthoma cells, correlate to the designation of the inflammatory type of undifferentiated pleomorphic sarcoma. **(Right)** The inflammatory cell infiltrate may obscure the neoplastic cells. The vascular pattern may include a staghorn (hemangiopericytoma-like) configuration [4].

Sinonasal Undifferentiated Pleomorphic Sarcoma, Myxoid Variant



Myxoid Variant With Curvilinear Vessels



(Left) The myxoid variant includes at least 50% of the tumor showing myxoid stroma [5]. The vascular component, composed of curvilinear capillary network, is noteworthy but not pathognomonic. **(Right)** The neoplastic and inflammatory cells condense along the arcing vessels. The curvilinear capillary network seen in the myxoid variant is also a feature seen in other sarcomas, in particular myxoid liposarcoma. Immunohistochemical staining is required to exclude alternative diagnoses.

Mesenchymal Chondrosarcoma

KEY FACTS

TERMINOLOGY

- Malignant mesenchymal tumor with cartilaginous differentiation
 - Biphasic tumor with 2 separate cell populations

CLINICAL ISSUES

- Rare: < 1% of head and neck chondrosarcomas
- Usually seen in 2nd and 3rd decades of life
- Most often in maxilla or mandible
- Radical surgical resection is preferred treatment
- Adjuvant therapy (radiation, chemotherapy) is of limited benefit in cartilaginous neoplasms of sinonasal tract

IMAGING

- CT shows moderate contrast enhancement and well-defined mass with multiple areas of fine and coarse calcification

MACROSCOPIC

- Must submit **all** tissue to document cartilage

MICROSCOPIC

- Cartilage is frequently limited and difficult to identify, requiring additional sections or levels
- Biphasic microscopic pattern
- Abrupt islands of cellular hyaline cartilage
- Small, undifferentiated round to spindled cells
- Cell arranged in solid pattern with staghorn-shaped vessels

ANCILLARY TESTS

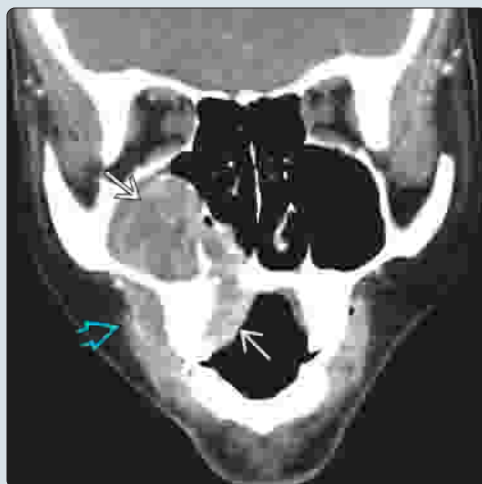
- Small cells **positive**: CD99, Sox9; **negative**: FLI-1
- Small round to spindled cells S100 protein negative, while cartilaginous component may be positive
- *HEY1-NCOA2* fusion detected by FISH in 75-80%

TOP DIFFERENTIAL DIAGNOSES

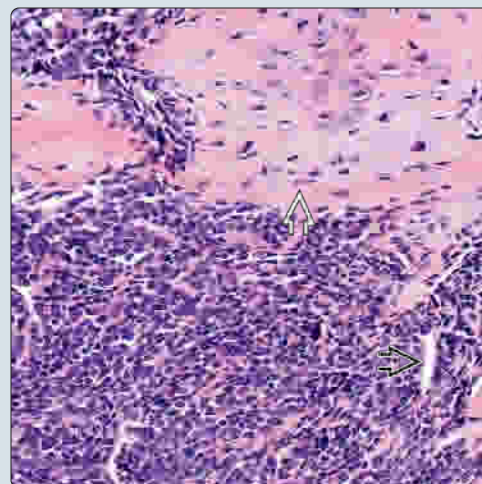
- Ewing sarcoma/PNET, rhabdomyosarcoma, olfactory neuroblastoma, small cell osteosarcoma, infantile myofibroma, hemangiopericytoma, synovial sarcoma

CT of Mesenchymal Chondrosarcoma

(Left) There is a large mass affecting the maxillary sinus, maxilla, and palate of this patient. Note the soft tissue extension. Bright signal calcifications are noted throughout the lesion. (Right) There is an island of abrupt cartilaginous differentiation immediately associated with a small, round to spindled, immature population arranged between the staghorn vessels.

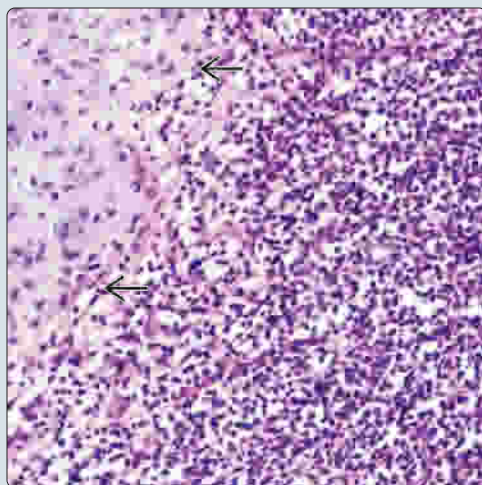


Biphasic Appearance of Mesenchymal Chondrosarcoma

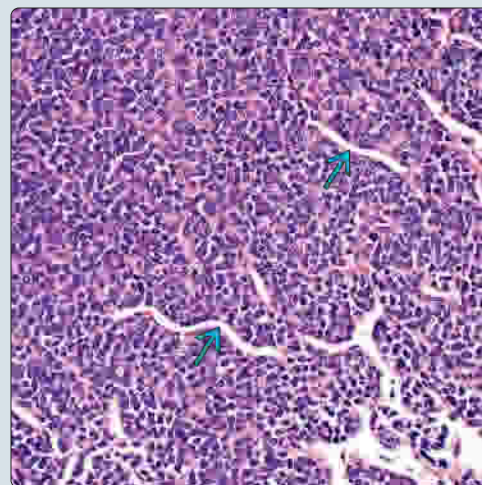


Cartilage Juxtaposed to Immature Cells

(Left) High-power view shows small round blue cells in nests and sheets juxtaposed to the cartilage. The cartilage shows atypia, as would be expected with a chondrosarcoma. (Right) Staghorn vessels are noted within the primitive small round blue cell proliferation. Cartilage is not seen in this field, but is required for the diagnosis.



Hemangiopericytoma-Like Pattern



TERMINOLOGY

Definitions

- Malignant mesenchymal tumor with cartilaginous differentiation
 - Biphasic tumor with 2 separate cell populations

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare: < 1% of head and neck chondrosarcomas
- Age
 - Affects all ages
 - Usually seen in 2nd and 3rd decades of life
- Sex
 - Equal gender distribution

Site

- Most often in maxilla or mandible
 - May occur in sinonasal tract and orbit

Presentation

- Nonspecific symptoms
 - Mass, teeth displacement, nasal obstruction, epistaxis
- Usually no history of radiation exposure

Treatment

- Radical surgical resection is preferred treatment
- Adjuvant therapy (radiation, chemotherapy) is of limited benefit in cartilaginous neoplasms of sinonasal tract
- Moderate to high risk of recurrence, due to anatomy and difficulty obtaining adequate margins

Prognosis

- More favorable for jaw tumors compared to other sites
- Varies from complete tumor response and long-term survival to rapid local tumor progression
- When metastases are present, usually widespread to lungs and bones
 - Demise in months
- Overall survival guarded
 - 5-year survival (55%), 10-year survival (27%)

IMAGING

Radiographic Findings

- No radiographic findings are pathognomonic for chondrosarcoma

MR Findings

- T1-weighted images after gadolinium contrast show inhomogeneous enhancement in calcified and uncalcified areas

CT Findings

- Moderate contrast enhancement and well-defined mass with multiple areas of fine and coarse calcification

Bone Scan

- Will be "hot" (positive)

MACROSCOPIC

General Features

- Similar to conventional chondrosarcoma
- Fleishy areas indicating small cell spindle component

Sections to Be Submitted

- Must submit **all** tissue to document cartilage

Size

- 2-10 cm

MICROSCOPIC

Histologic Features

- Cartilage is frequently limited and difficult to identify, requiring additional sections or levels
- Biphasic microscopic pattern
 - Abrupt islands of cellular hyaline cartilage
 - Small, undifferentiated, round to spindled cells
- Cell arranged in solid pattern with staghorn-shaped vessels

ANCILLARY TESTS

Immunohistochemistry

- Small cells **positive**: CD99, SOX9; **negative**: FLI-1
- Small round to spindled cells S100 protein negative, while cartilaginous component may be positive

Genetic Testing

- *HEY1-NCOA2* fusion detected by FISH in 75-80%
 - *HEY1* is downstream effector of Notch signaling
 - *NCOA2* is member of p160 nuclear hormone receptor transcriptional coactivator family

DIFFERENTIAL DIAGNOSIS

Small Cell Neoplasms

- When cartilaginous component is absent (not sampled), small cell neoplasms are considered
 - Ewing sarcoma/PNET, rhabdomyosarcoma, olfactory neuroblastoma, small cell osteosarcoma, neuroendocrine carcinoma (small cell or large cell), desmoplastic small cell tumor, infantile myofibroma separated by specific immunohistochemistry and molecular results
 - Leukemic deposits (granulocytic sarcoma) and malignant lymphoma
- Hemangiopericytoma
- Synovial sarcoma

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Angiosarcoma

KEY FACTS

TERMINOLOGY

- High-grade malignant vascular neoplasm

CLINICAL ISSUES

- ~ 50% of all angiosarcomas develop in head and neck
 - Nasal cavity alone most often
- Male > female (2:1); females tend to be younger than males at presentation
- Epistaxis is most common symptom
- No syndrome association, specifically Kasabach-Merritt
- Best outcome achieved with combination of surgery, radiation, and chemotherapy

MACROSCOPIC

- Polypoid, soft to friable masses with hemorrhage and necrosis
- Range: 0.7-8 cm (mean: 4 cm)

MICROSCOPIC

- Ulcerated surface epithelium (usually respiratory type)
- Necrosis and hemorrhage prominent
- Freely anastomosing vascular channels
- Tortuous, irregular, small to large, and cleft-like spaces
- Atypical, enlarged, spindled to epithelioid endothelial cells line channels
- Intracytoplasmic vacuoles or neolumen
- Extravasated erythrocytes are noted throughout
- Increased mitotic figures, including atypical forms
- Extracellular eosinophilic hyaline globules are absent

ANCILLARY TESTS

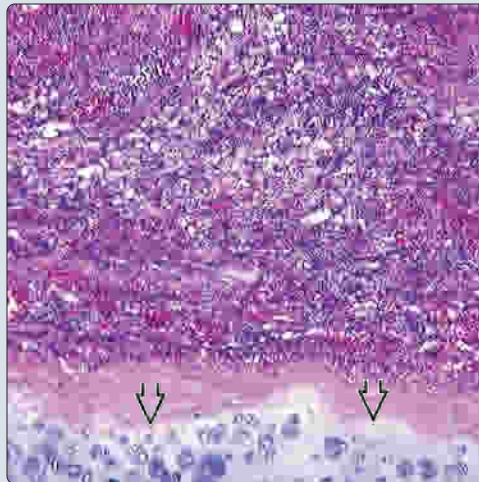
- **Positive:** CD31, CD34, FVIIIIRAg, ERB, FLI1, Claudin-5

TOP DIFFERENTIAL DIAGNOSES

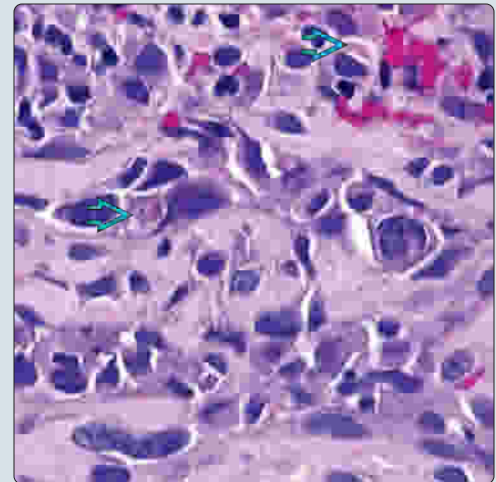
- Granulation tissue, lobular capillary hemangioma, juvenile nasopharyngeal angiofibroma, epithelioid hemangioma, Kaposi sarcoma

(Left) Hematoxylin and eosin shows a highly cellular vascular neoplasm with extravasated erythrocytes adjacent to septal cartilage. This pattern and cellularity is very suspicious for an angiosarcoma. **(Right)** Hematoxylin and eosin shows highly pleomorphic cells projecting into slit-like lumens. A neolumen formation is present. True neolumen formation is seen in neoplasia only.

Vascular Neoplasm Adjacent to Cartilage

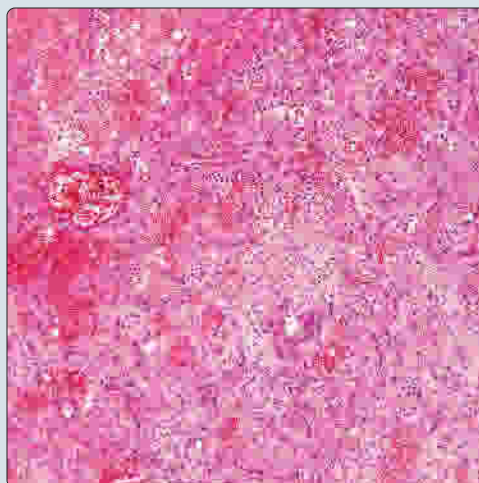


Neolumen Formation

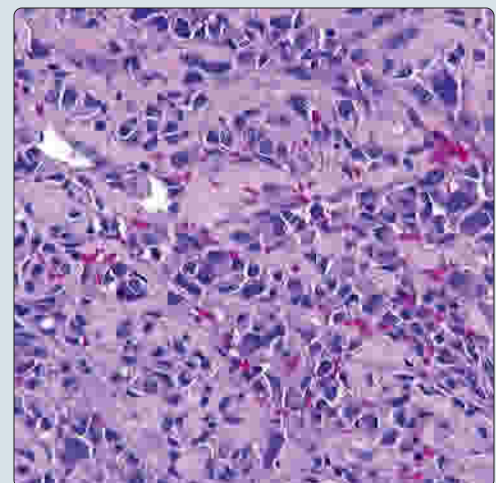


(Left) Hematoxylin and eosin shows hemorrhagic and degenerated material within an angiosarcoma. Pleomorphism is noted, even at this low magnification. This amount of hemorrhage would be detected grossly. **(Right)** Hematoxylin and eosin shows a cellular pleomorphic population arranged in a haphazard distribution, lining the irregular, freely anastomosing vascular channels, which are filled with extravasated erythrocytes.

Hemorrhagic Background



Pleomorphism in Angiosarcoma



TERMINOLOGY

Synonyms

- Epithelioid hemangioendothelioma, malignant hemangioendothelioma, malignant angioendothelioma, lymphangiosarcoma, hemangiosarcoma, hemangioblastoma

Definitions

- High-grade malignant vascular neoplasm

ETIOLOGY/PATHOGENESIS

Radiation

- May result in tumor development after long latent period

Environmental Exposure

- Chemicals have not been reported to result in tumor development

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare, < 0.1% of all sinonasal tract malignancies
 - ~ 50% of all angiosarcomas develop in head and neck
 - Most common in scalp skin and superficial soft tissues
- Age
 - Mean: 47 years
 - Range: 8-82 years
 - Females tend to be younger than males at presentation
- Sex
 - Male > female (2:1)

Site

- Nasal cavity alone most often, but may involve paranasal sinuses

Presentation

- Epistaxis is most common symptom
- Nasal discharge &/or obstruction
- No syndrome association, specifically Kasabach-Merritt

Treatment

- Options, risks, complications
 - Best outcome achieved with combination of surgery, radiation, and chemotherapy
- Surgical approaches
 - Wide surgical excision
- Adjuvant therapy
 - Multiagent chemotherapy
- Radiation
 - Postoperative radiation

Prognosis

- Generally poor
 - ~ 60% die from disease in ~ 2 years
 - Better prognosis than skin or soft tissue sarcomas, perhaps due to earlier detection
- Recurrences are common, up to 40%
- Metastatic disease identified in lung, liver, spleen, and bone marrow
- Poor prognosis associated with

- Female patients have worse prognosis (increased percentage of patients die from disease), although overall length of survival is identical to male patients
- Older patients than younger patients
- Larger tumors &/or tumors from maxillary sinus
- Patients with radiation exposure

IMAGING

General Features

- Radiolucent or radiopaque density associated with destructive growth in soft tissue, cartilage, &/or bone
- CT determines extent of tumor (contrast-enhanced mass)
- MR shows bright mass on T2-weighted images
- Angiography identifies extent of tumor and shows feeder vessel(s), allowing for presurgical angiographic embolization, if desired

MACROSCOPIC

General Features

- Nodular, polypoid, soft to friable masses
- Red to purple with hemorrhage and necrosis

Size

- Range: 0.7-8 cm (mean: 4 cm)
- Tumors in female patients tend to be larger (6 cm vs. 3 cm)
- Paranasal sinus tumors tend to be larger than nasal cavity tumors (6.8 cm vs. 2.2 cm)

MICROSCOPIC

Histologic Features

- Ulcerated surface epithelium (usually respiratory type)
- Necrosis and hemorrhage prominent
- Infiltrative neoplasm into surrounding soft and hard tissues
- Extravasated erythrocytes are noted throughout
- Freely anastomosing vascular channels
 - Tortuous, irregular, small to large, and cleft-like spaces
- Atypical, enlarged, spindled to epithelioid endothelial cells line channels
 - Endothelial cells may be single, multilayered or papillary, tufted
- Intracytoplasmic vacuoles or neolumen
 - Frequently contain erythrocytes
- Nuclear chromatin is heavy, coarse, with irregular nuclear contours
- Increased mitotic figures, including atypical forms
- Extracellular eosinophilic hyaline globules are absent
- Inflammatory cells are present but may depend on ulceration and reaction

ANCILLARY TESTS

Immunohistochemistry

- **Positive** with variety of vascular markers

DIFFERENTIAL DIAGNOSIS

Granulation Tissue

- Proliferation of vessels arranged perpendicular to surface with plump endothelial cells

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CD34	Positive	Cytoplasmic	> 98% of neoplastic cells
CD31	Positive	Cytoplasmic	> 95% of neoplastic cells
FVIIIIRAg	Positive	Cytoplasmic	> 90% of neoplastic cells
Claudin-5	Positive	Cytoplasmic	Strong and diffuse reaction
ERG	Positive	Nuclear	> 95% of neoplastic cells
FLI-1	Positive	Nuclear	Strong and diffuse nuclear reaction
Actin-sm	Positive	Cytoplasmic	Adjacent to vascular spaces
Ki-67	Positive	Nuclear	> 10% of cells
EMA	Positive	Cell membrane	Variably reactive
CK-PAN	Negative		
S100	Negative		
Actin-HHF-35	Equivocal	Cytoplasmic	Variably reactive

- Ulcerated surface is common, with mixed inflammatory infiltrate and prominent histiocytes
- No cytologic atypia, freely anastomosing vessels, or atypical mitotic figures

Lobular Capillary Hemangioma

- Polypoid mass with surface ulceration and fibrinoid necrosis
- Lobular architecture with central perpendicular vessels with surrounding capillaries
- Plump endothelial cells with bland nuclei and brisk mitotic index
- Edematous to fibrotic stroma with hemosiderin-laden macrophages
- Variable inflammatory infiltrate

Juvenile Nasopharyngeal Angiofibroma

- Arises in nasopharynx in young male patients exclusively
- Cellular and richly vascularized mesenchymal neoplasm
- Background fibrous connective tissue stroma with many variably sized, disorganized vessels of varying thickness with patchy muscle content
- Plump endothelial cells without atypia
- Elastic tissue is lacking in vessel walls

Epithelioid Hemangioma

- Also called angiolymphoid hyperplasia with eosinophilia or histiocytoid hemangioma
- Extranodal proliferation of vessels associated with heavy nodular to diffuse lymphocytic infiltrate with eosinophils
- Enlarged nonatypical endothelial cells protruding into lumen in cobblestone or hobnail-type fashion, often occluding vessel lumen

Glomangiopericytoma

- Diffuse syncytial growth of closely packed round to oval cells
- Arranged in short interlacing fascicles, which are richly vascularized
- Capillary to large patulous spaces that may have ramifying staghorn configuration
- Prominent peritheliomatous hyalinization
- Extravasated erythrocytes, mast cells, and eosinophils

- Positive with actins and β -catenin but not with vascular markers

Kaposi Sarcoma

- Plaque-tumor stage shows sieve-like vasoformative pattern
- Slightly atypical spindled tumor cells with eosinophilic, glassy-hyaline intra- and extracellular globules (PAS[+])
- HHV8 is usually positive, helping to confirm diagnosis

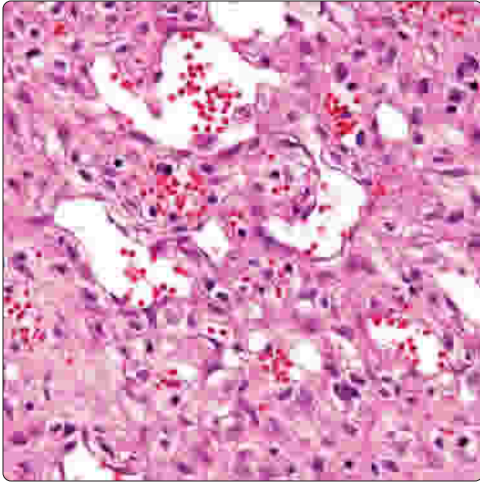
Thrombosed Vessel

- Recanalization of thrombosed vessels (Masson vegetant endothelial hyperplasia or intravascular papillary endothelial hyperplasia)
- No atypia of endothelial cells as they line papillary projections within organizing spaces

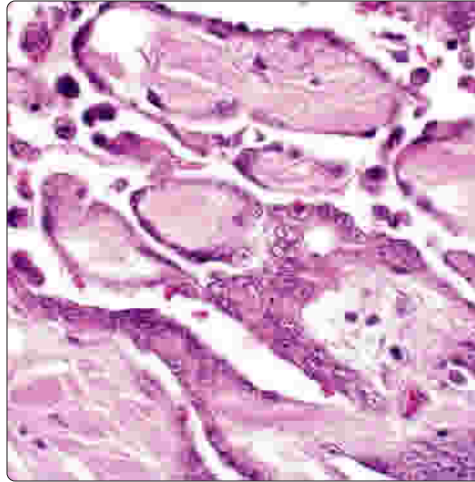
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Variable Vascular Channels

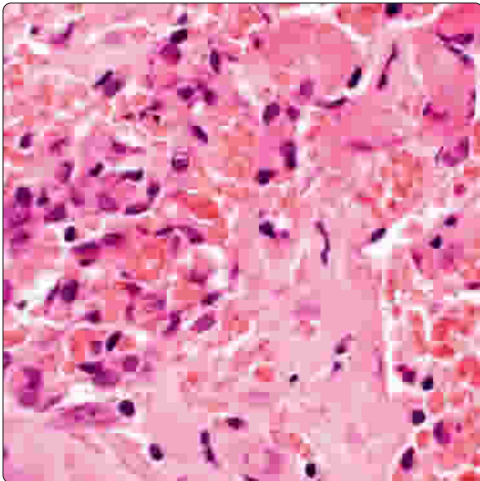


Epithelioid Angiosarcoma

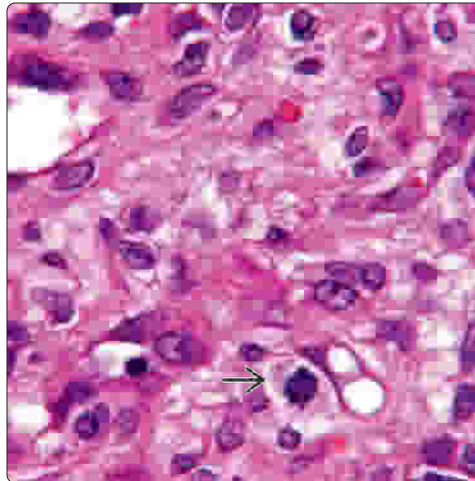


(Left) Hematoxylin and eosin shows variably sized vascular channels associated with a neoplastic proliferation of atypical endothelial cells. Erythrocytes are noted throughout. (Right) The endothelial cells in this angiosarcoma show an epithelioid appearance. The nuclei are vesicular and open, with prominent nucleoli.

Anastomosing Vascular Channels

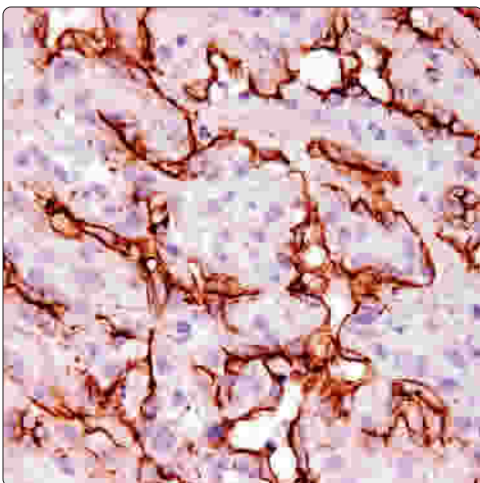


Mitotic Figure

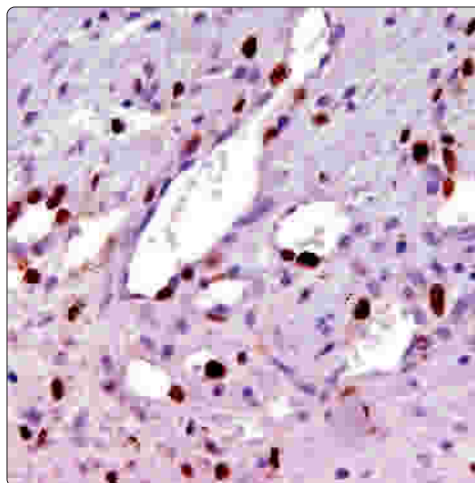


(Left) Hematoxylin and eosin shows a hobnail or tufted pattern of endothelial cells projecting into vascular spaces filled with erythrocytes. (Right) Mitoses are usually easy to identify in angiosarcoma. However, mitoses can be seen in reactive vascular proliferations also.

CD34 Highlights Neoplastic Cells



High Ki-67 Proliferation Index



(Left) CD34 shows strong reactivity in the cytoplasm of the endothelial cells arranged in an anastomosing pattern. (Right) Ki-67 shows a positive reaction within the nuclei of the endothelial cells in the stroma, as well as lining the vascular spaces.

KEY FACTS

TERMINOLOGY

- Polymorphic neoplastic infiltrate with
 - Angioinvasion &/or angiodestruction
 - CD2(+), surface CD3(-), cytoplasmic CD3ε(+), CD56(+) phenotype
 - Strong association with EBV

ETIOLOGY/PATHOGENESIS

- EBV identified in > 95% of cases
 - Irrespective of ethnic background, NK-/T-cell lymphoma, nasal type is strongly associated with EBV

CLINICAL ISSUES

- Extranodal NK-/T-cell lymphomas, nasal type represents most common type of lymphoma in sinonasal tract
 - Most commonly affects nasal cavity
- Destructive process of midfacial region
- Treatment varies depending on extent of disease
 - Radiotherapy for localized disease

- Aggressive chemotherapy in disseminated disease
- 5-year survival: 46%
 - Median survival: 4.2 years
- Local recurrence/relapse and systemic failure is common

MICROSCOPIC

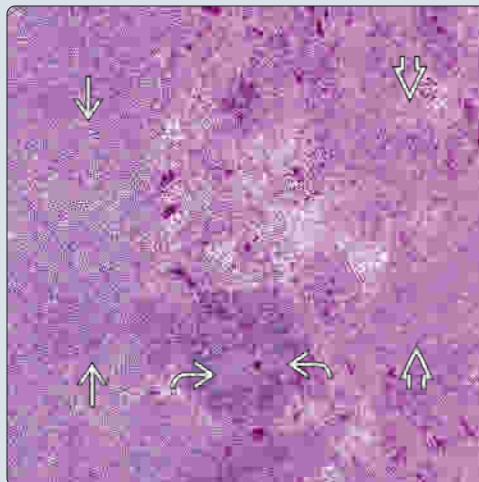
- Polymorphic neoplastic infiltrate with angioinvasive and angiodestructive pattern
- Broad cytologic spectrum
- Angiocentric and angiodestructive pattern
- Presence of geographic (ischemic type) necrosis
- Presence of EBV, even in absence of malignant cellular process, supportive of diagnosis

ANCILLARY TESTS

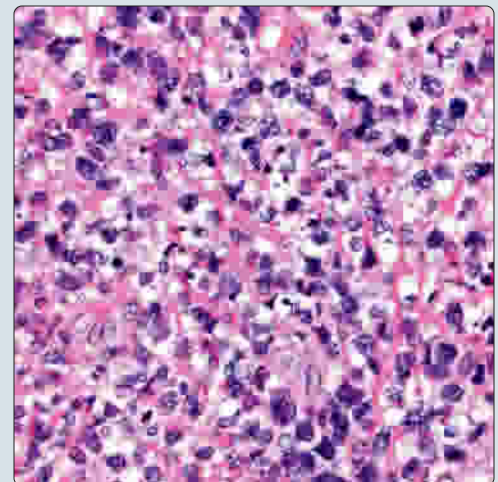
- NK-cell immunophenotype is most commonly present, including cytoplasmic CD2(+), cytoplasmic CD3(+), CD56(+)
- Expression of granzyme B, TIA-1, perforin
- EBER(+)

Confluent Foci of Necrosis

(Left) At low magnification, ischemic-type (geographic) necrosis is present [1] adjacent to an area of viable tumor [2] and obliterated vascular space [3]. The necrosis is in the depth of the tissue and not superficially located. (Right) Dyscohesive undifferentiated malignant cellular proliferation is comprised of medium to large cells with round to oval nuclei, vesicular to hyperchromatic chromatin, and eosinophilic to clear-appearing cytoplasm.

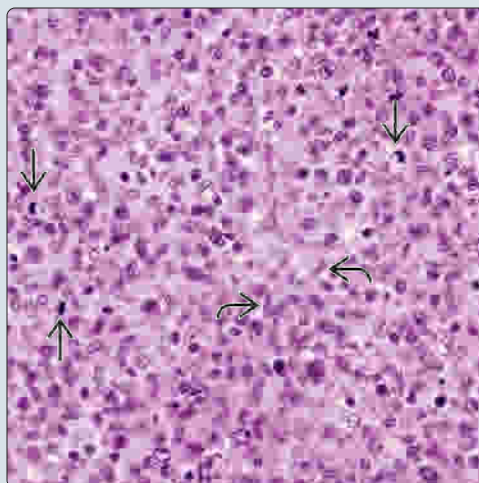


Dyscohesive Cellular Proliferation

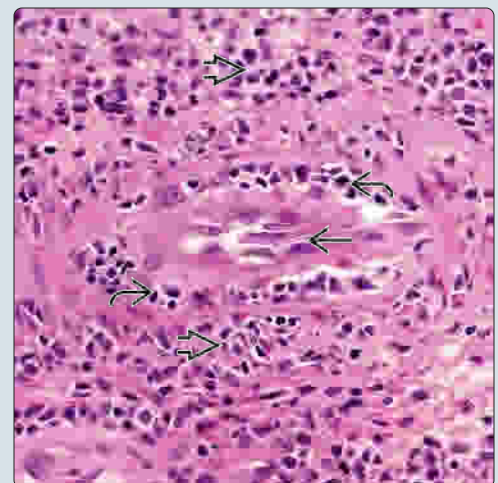


Diffuse Growth Pattern

(Left) Diffuse cellular proliferation is shown comprised of cells with varying size and shape, including cells with elongated convoluted appearing nuclei [1], vesicular to hyperchromatic chromatin, and indistinct eosinophilic to clear cytoplasm. Note the scattered mitotic figures [2]. (Right) The neoplastic cells surround (angiocentric) [3] and invade (angioinvasive) [4] an endothelial cell-lined [5] vascular space, resulting in ischemic-type necrosis, typically present in this neoplasm.



Angiocentric and Angioinvasive



TERMINOLOGY

Synonyms

- Angiocentric immunoproliferative lesions; peripheral T-cell lymphoma
- Angiocentric NK-/T-cell lymphoma of nasal type
- Polymorphic reticulosis
- Lethal midline granuloma
- Midline malignant reticulosis
- Idiopathic midline destructive disease
- Stewart granuloma
- World Health Organization classifies NK-cell tumors into 3 types
 - Extranodal NK-/T-cell lymphomas, nasal type
 - Extranodal NK-/T-cell lymphomas, nonnasal type
 - NK-cell leukemias

Definitions

- Polymorphic neoplastic infiltrate with
 - Angioinvasion &/or angiodestruction
 - CD2(+), cytoplasmic CD3(+), surface CD3(-), CD56(+) phenotype
 - Strong association with Epstein-Barr virus (EBV)

ETIOLOGY/PATHOGENESIS

Infectious Agents

- EBV identified in > 95% of cases
- Irrespective of ethnic background, NK-/T-cell lymphoma, nasal type is strongly associated with EBV

Immunosuppression

- Occurs with increased frequency in setting of immune suppression, especially after organ transplantation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Extranodal NK-/T-cell lymphomas, nasal type represents most common type of lymphoma in sinonasal tract
 - Prevalent in Asia and South America
 - Rare in Western countries
- Age
 - Disease of adults with median age in 6th decade
 - Closely related entity seen mainly in children is hydroa vacciniforme-like lymphoma
 - Also EBV positive
- Sex
 - Male > female
- Ethnicity
 - Most common in Asians
 - Reported with significant frequency in South and Central America and Mexico
 - In these populations, primarily occurs in individuals of Native American origin
 - Findings suggest racial predisposition
 - Although uncommon, occurs in Western populations in Caucasians

Site

- Most commonly affects nasal cavity

Presentation

- Destructive process of midfacial region with
 - Nasal septal destruction
 - Palatal destruction/perforation
 - Orbital swelling
 - Obstructive symptoms related to mass
 - Small percentage of cases present with hemophagocytic syndrome with pancytopenia
- Primary lymph node involvement is extremely uncommon
- Hyper-IgE syndrome (Job syndrome)
 - Rare primary immunodeficiency associated with increased risk for malignancies
 - Includes extranodal NK-/T-cell lymphoma

Laboratory Tests

- Serum EBV-DNA copy number useful as specific tumor marker
 - May be predictive prognostic factor
- Antineutrophil cytoplasmic antibodies (ANCA) and proteinase 3 (PR3) levels not elevated

Treatment

- Options, risks, complications
 - Treatment varies depending on extent of disease
 - Radiotherapy for localized disease
 - Aggressive chemotherapy in disseminated disease
 - Majority are localized at presentation (Ann Arbor stage IE/IIe) treated by radiation alone or chemoradiation
 - In some patients, surgical resection may be needed for symptomatic relief (e.g., airway obstruction)
- Adjuvant therapy
 - Many stage I/II patients treated with radiotherapy fail systemically, implying that concomitant chemotherapy may be needed
 - Chemotherapy is indicated for advanced nasal NK-cell lymphoma and nonnasal and aggressive subtypes
 - Treatment results are unsatisfactory
 - High-dose chemotherapy with hematopoietic stem cell transplantation may be beneficial to selected patients
 - Therapeutic approaches to advanced stage or relapsed and refractory disease not well established
- Radiation
 - Radiosensitive tumors but prognosis is generally poor once dissemination occurs
 - First-line radiotherapy most important key to successful treatment
 - Early radiation is advocated for localized nasal-type NK-/T-cell lymphoma
 - Effectiveness of radiotherapy evident in limited disease but questionable in extensive disease

Prognosis

- 5-year survival: 46%
 - Median survival was 4.2 years
- Local recurrence/relapse and systemic failure is common
 - Systemic failure includes increased risk of dissemination to skin, testes, and GI tract
- Favorable prognostic factors include
 - Limited local invasion
 - Low international prognostic index score
 - Lack of B symptoms

Extranodal NK-/T-Cell Lymphoma, Nasal Type

- Low proliferation indices as determined by Ki-67 (MIB1) staining
- Lower EBV viral load in tumor tissue & lower serum EBV-DNA
- Poor prognostic factors include
 - Extensive local invasion (to skin, bone)
 - Poor performance score (Eastern Cooperative Oncology Group [ECOG] of 2 or higher),
 - Presence of B symptoms & regional lymphadenopathy
 - High proliferation rate
 - Bulky disease
 - High lactate dehydrogenase level
 - Development of hemophagocytic syndrome, uncommon complication seen in ~ 10% of cases, is considered fatal

IMAGING

Radiographic Findings

- Locally destructive disease typically presenting with obliteration of nasal passages and maxillary sinuses
- Involvement of adjacent anatomic structures (e.g., alveolar bone, hard palate, orbits, nasopharynx) associated with extensive soft tissue masses present in majority of cases

MICROSCOPIC

Histologic Features

- Polymorphic neoplastic infiltrate with angioinvasive and angiodestructive pattern
- Broad cytologic spectrum
 - Usually (but not always) cytologically atypical cells are present
 - Vary from small and medium-sized cells to large, hyperchromatic cells with
 - Nuclear pleomorphism, irregular and elongated nuclei, prominent nucleoli, eosinophilic to clear cytoplasm
 - Early phase of disease may not include overtly malignant-appearing cells
 - Infiltrate appears nonspecific, including admixture of chronic inflammatory cells
 - Disconnect between destructive clinical process and absence of overtly malignant infiltrate
 - Presence of EBV, even in absence of malignant cellular process, supportive of diagnosis
 - EBV-positive cells are typically absent in nasal cavity mucosa &/or in inflammatory sinonasal diseases
- Increased mitotic activity, including atypical mitoses, often present
- Epitheliotropism and pseudoepitheliomatous hyperplasia may be present
- Associated prominent admixed inflammatory cell infiltrate may be present
 - Polymorphous inflammatory cell infiltrate may obscure atypical cells
 - Benign inflammatory cell infiltrate includes lymphocytes, plasma cells, histiocytes, and eosinophils
 - Multinucleated giant cells and granulomas absent
- Angiocentric and angiodestructive pattern
 - Atypical cells invade and destroy blood vessels
 - Tumor cells around and within vascular spaces with infiltration and destruction of vessel wall

- Perivascular localization alone insufficient for designation of angiocentricity
- Vascular invasion and destruction responsible for designation of angiocentric lymphoma

- Presence of geographic (ischemic-type) necrosis characterized by
 - Tissue destruction with bluish or gritty appearance
 - Necrosis is virtually constant (but not pathognomonic) feature
 - Zonal pattern of distribution suggests vascular pathogenesis

ANCILLARY TESTS

Histochemistry

- Elastic stains may be useful in identification of angiocentric/angioinvasive growth
 - Disruption of elastic membrane with permeation of vessel wall by neoplastic cells
- Stains for microorganisms are negative

Immunohistochemistry

- NK-cell immunophenotype is most commonly present, including
 - CD2 positive
 - Cytoplasmic CD3 positive, but surface (membranous) CD3 (by flow cytometry) negative
 - CD56 (neural cell adhesion molecule [NCAM]) positive
- Markers of cytotoxic granules are positive, including expression of
 - Granzyme B, cytotoxic granule-associated TIA-1, perforin
- CD4, CD5, CD8, CD20, CD57 (Leu-7) are negative
- T-cell markers, including CD43 and CD45RO (UCHL1) are positive
- Some cases may be CD30 positive
- p63 usually negative but may be focally positive
- T-cell receptor (TCR) and immunoglobulin (Ig) genes are germline (NK lineage)
 - T lineage cases have clonally arranged TCR genes and may express surface CD3
- T-cell lineage in ~ 25-35% of cases
 - CD2(+), cytoplasmic CD3(+), CD5(+), CD8(+/-), CD56(-/+), cytotoxic markers (+)
- CD45RB (leucocyte common antigen) positive
- Tumors CD56 negative may still be classified as NK-/T-cell lymphomas if they
 - Express T-cell markers
 - Express cytotoxic markers
 - Are EBV positive
- EBV
 - Detected in most neoplastic cells in virtually all cases by in situ hybridization for EBV-encoded RNA (EBER)
 - Some cases may express EBV latent membrane protein (LMP), but LMP is less sensitive than EBER in detecting EBV
- Vimentin positive
- Negative for epithelial markers (cytokeratins), melanocytic markers, neuroendocrine markers, mesenchymal myogenic markers

Genetic Testing

- Clonal EBV infection almost invariably present (> 95% of cases)
 - Since EBV-positive cells are typically absent in nasal cavity mucosa or in inflammatory diseases of nasal cavity, presence of EBV can be used in conjunction with light microscopy in diagnosis of nasal cavity NK-/T-cell lymphomas
 - Identification of EBV would confer diagnosis of NK-/T-cell lymphoma, nasal type even in cases without overtly atypical/malignant-appearing cells
- *TCR* gene rearrangement
 - Present in T-cell tumors
 - T-cell receptor gene is germline
 - NK-cell tumors do not carry *TCR* gene rearrangements

DIFFERENTIAL DIAGNOSIS

Nonspecific Chronic Sinusitis

- Innocuous clinical symptoms lacking destructive nature of NK-/T-cell lymphoma, nasal type
- EBV negative

Granulomatosis With Polyangiitis

- Mixed inflammatory infiltrate, scattered multinucleated giant cells, vasculitis
- Elevated ANCA, PR3
- EBV negative

Sinonasal B-Cell Lymphoma

- Most often diffuse large B-cell lymphoma
 - Submucosal diffuse cellular infiltrate of monotonous population of large cells
- Less commonly shows angiocentricity and angioinvasion compared to NK-/T-cell lymphoma, nasal type
- Immunophenotype is B cell, including
 - CD20(+)
 - CD79-a(+)
 - CD3(-)
- Molecular evaluation shows
 - Monoclonal *IgH* gene rearrangements
- EBV negative

Carcinomas

- Immunoreactive for cytokeratins
- Nonreactive for hematolymphoid markers
- EBV negative

Olfactory Neuroblastoma, High Grade

- Immunoreactive for neuron-specific enolase, neuroendocrine markers, S100 protein, including peripheral sustentacular cell-type pattern, calretinin
- EBV negative

Mucosal Malignant Melanoma

- Immunoreactive for vimentin and melanocytic markers
- EBV negative

Small Cell Neuroendocrine Carcinoma

- Immunoreactive for cytokeratins, CD56, neuroendocrine markers
 - Chromogranin
 - Synaptophysin

- CD57

- EBV negative

Rhabdomyosarcoma

- Immunoreactive for desmin, myoglobin, myogenin, and vimentin
- EBV negative

Primitive (Peripheral) Neuroectodermal Tumor/Extrasosseous Ewing Sarcoma

- Immunoreactive for FLI-1, CD99; variable reactivity for neuroendocrine markers, neuron-specific enolase, epithelial markers
- EBV negative

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Clinical features are of major importance in defining NK-/T-cell lymphoma

Pathologic Interpretation Pearls

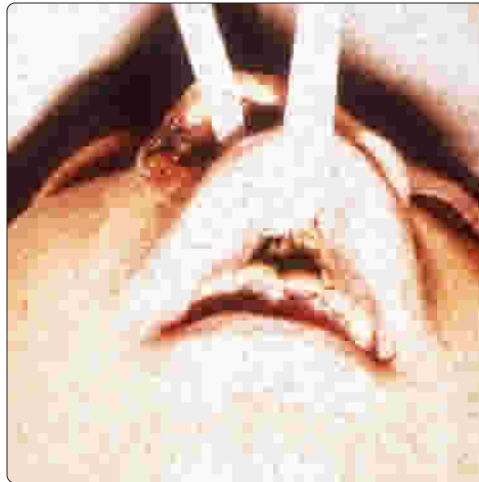
- Presence of EBV confirmatory of diagnosis even in situation where cellular infiltrate not overly malignant
 - EBV-positive cells typically absent in nasal cavity mucosa or in inflammatory diseases of nasal cavity

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Destructive Process

(Left) Clinically, NK-/T-cell lymphoma is often a destructive process of the midfacial region that may include facial deformities due to destruction of bony walls between adjacent anatomic sites. (Right) CT scan shows a destructive nasal cavity mass with almost completely opacified maxillary sinus and thickening of mucosa in the nasopharynx. This patient was shown to have extranodal NK-/T-cell lymphoma, nasal type.

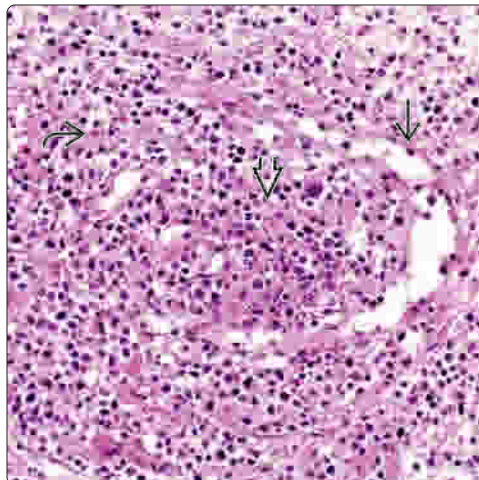


NK-/T-Cell Lymphoma, Imaging Findings

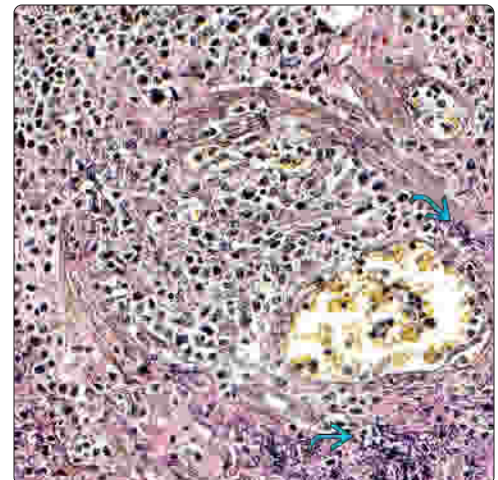


Intravascular Thrombus-Like Growth

(Left) The neoplastic cells surround (angiocentric) and invade (angioinvasion) vascular spaces with near obliteration of the endothelial cell-lined vascular lumen with thrombus-like effects. The results of vascular compromise will be ischemic-type necrosis (not shown). (Right) The presence of vasculitis can be difficult to identify and elastic staining (EVG) may assist in showing disruption of elastic membranes due to tumor permeation/invasion through the wall with plugging of the vessel lumen.

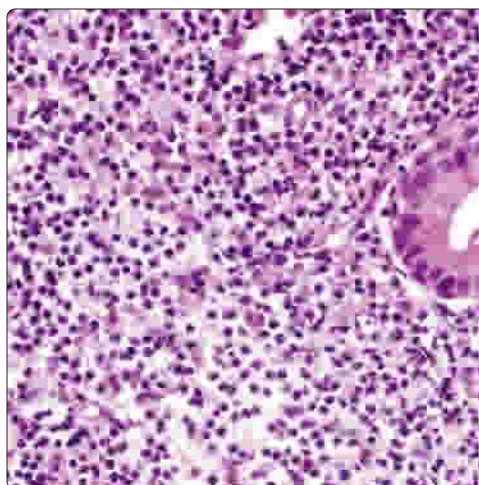


Elastic Stain, Disrupted Elastic Membranes

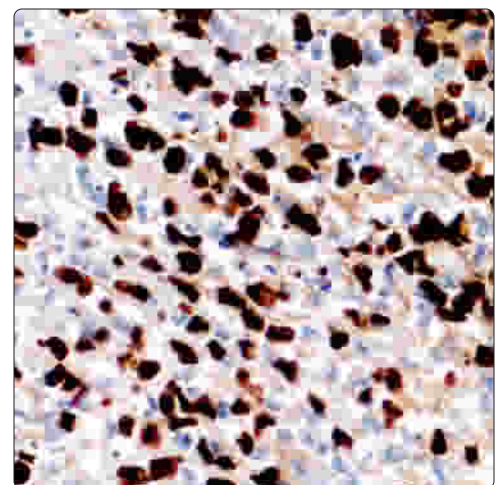


Bland-Appearing Cytomorphology

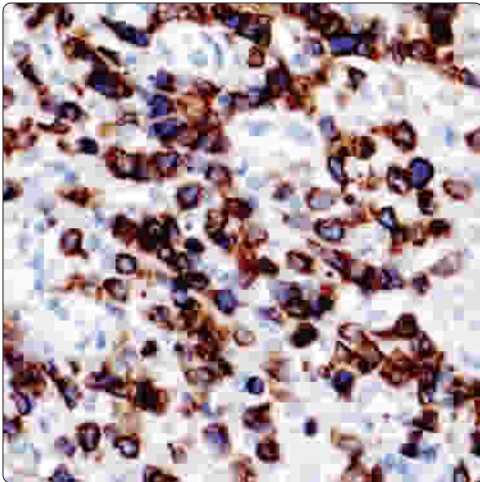
(Left) In spite of aggressive clinical behavior, the histology in any given case may include a polymorphous cell population lacking overtly malignant cytomorphic features. In such cases, EBV staining would support a diagnosis of NK-/T-cell lymphoma. (Right) Diffuse EBER reactivity is present that, even in the absence of cytomorphic malignant features, would support a diagnosis of NK-/T-cell lymphoma. Relative to sinonasal lesions/neoplasms, EBV is uniquely identified in NK-/T-cell lymphoma.



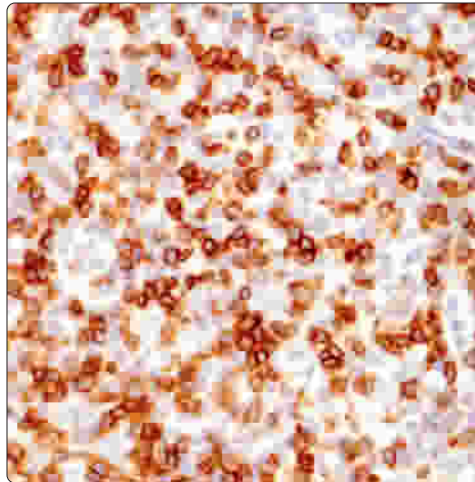
EBV(+) Cells



CD2 Expression

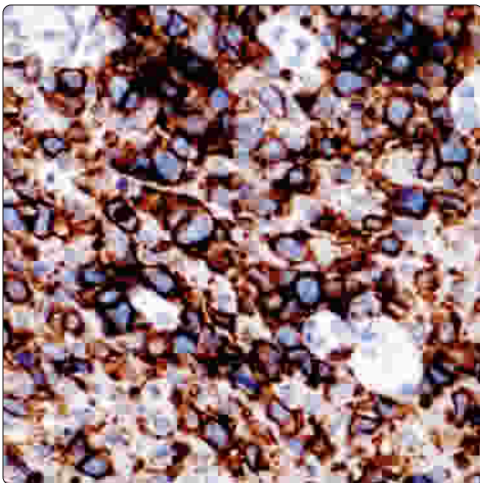


CD3 Expression

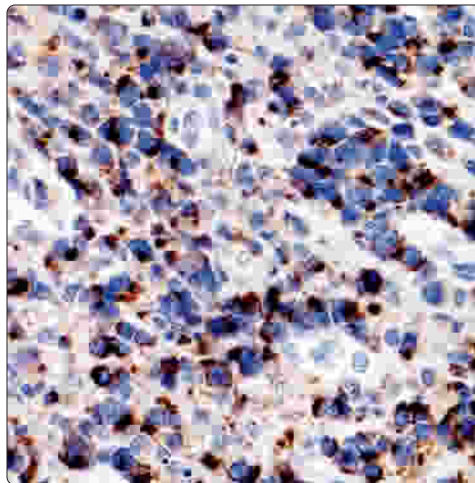


(Left) The lesional cells of NK-/T-cell lymphoma are immunoreactive for CD2 as well as for hematolymphoid markers (e.g., CD45 or leucocyte common antigen [not shown]). **(Right)** Diffuse CD3 (cytoplasmic, not surface) positive neoplastic cells are present. NK-cell lineage is the most common immunophenotype, seen in approximately 65-75% of cases, and characterized by CD2(+), cytoplasmic CD3ε(+), CD56(+), and expression of cytotoxic markers.

CD56 Expression

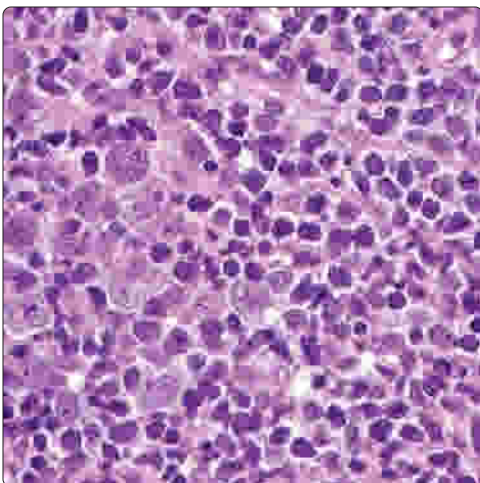


TIA1 Expression

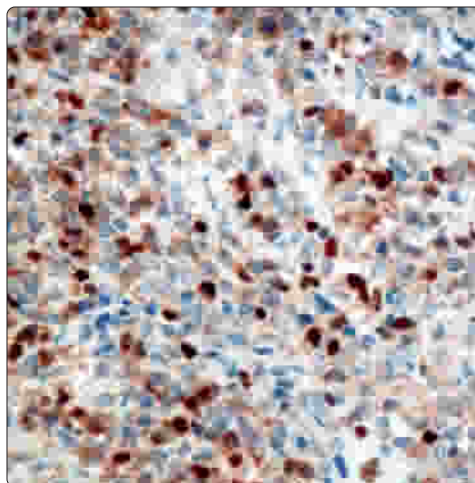


(Left) The neoplastic cells are diffusely immunoreactive for CD56. **(Right)** The neoplastic cells are diffusely immunoreactive for the cytotoxic granule marker TIA1. Given overlapping of light microscopic features shared among sinonasal undifferentiated malignant neoplasms, especially in limited biopsy material, a broad immunohistochemical antigenic panel is required in the diagnosis and differential diagnosis of these neoplasms, including but not limited to NK-/T-cell lymphoma.

Sinonasal Undifferentiated Malignancy



p63 Expression in NK-/T-Cell Lymphoma



(Left) Biopsy of a nasal cavity lesion shows undifferentiated malignant cells that could represent any number of sinonasal tract neoplasms. **(Right)** In conjunction with the light microscopic features seen in the adjacent image, the presence of p63 staining may result in an erroneous diagnosis of a carcinoma. NK-/T-cell lymphomas may show scattered p63(+) cells; in contrast, carcinomas are typically diffusely p63(+), and are not always positive for cytokeratins.

Biphenotypic Sinonasal Sarcoma

KEY FACTS

TERMINOLOGY

- Biphenotypic sinonasal sarcoma (BSNS)
- Low-grade spindle cell neoplasm of sinonasal tract associated with respiratory epithelium and showing S100 protein and actin reactivity

CLINICAL ISSUES

- Range: 24-85 years; mean: 52 years
- Female > males (3:1)
- Multiple sites affected, often with extension into orbit (25%) or through cribriform plate (11%)
- Local recurrences common (44%), between 1-9 years after presentation
- No patient has yet been reported to die of disease

MICROSCOPIC

- Highly cellular spindled cell population with infiltrative pattern, including bone invasion (21%)
- Medium to long fascicles, with herringbone pattern

- Highly uniform cells with elongated nuclei; focally wavy
- Concurrent surface-type respiratory epithelial proliferation invaginated from surface or in small cystic spaces within proliferation
- Glandular structures intimately associated with spindled cells in several areas


ANCILLARY TESTS

- S100 protein: Focal, patchy to diffuse in all tumors
- SMA or MSA seen in nearly all tumors, but strong and diffuse reaction with SMA seen in only ~ 50% of cases
- t(2;4)(q35;q31.1): *PAX3-MAML3* fusion protein

TOP DIFFERENTIAL DIAGNOSES

- Fibrosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor (including Triton tumor), leiomyosarcoma, mucosal melanoma, glomangiopericytoma, solitary fibrous tumor, schwannoma, respiratory epithelial adenomatoid hamartoma

Respiratory Epithelial Islands in Spindle Cell Proliferation

(Left) A highly cellular, but monotonous, population of spindled cells comprise the bulk of the tumor in biphenotypic sinonasal sarcoma (BSNS). There are numerous invaginations of surface respiratory epithelium, as well as small glandular profiles . (Right) There is a unique juxtaposition of a respiratory-type epithelial proliferation within the monotonous spindled cell tumor in a BSNS. This relationship is unique to this tumor.

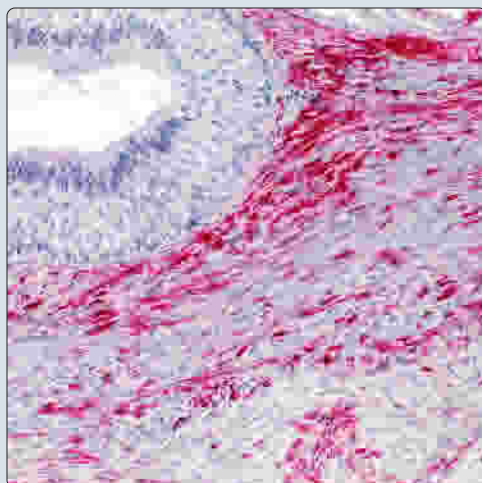


Epithelial Proliferation and Spindled Cell Population

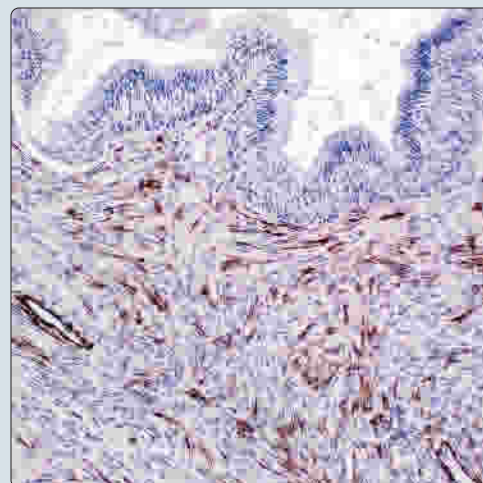


S100 Protein Reaction

(Left) The spindled cell population shows a strong, but patchy, nuclear and cytoplasmic reaction with S100 protein. The epithelial elements are negative. (Right) The smooth muscle actin shows a strong, but patchy, reaction in many of the neoplastic cells in this tumor. Note the prominent internal control seen in the vessels.



SMA Reaction



TERMINOLOGY

Abbreviations

- Biphenotypic sinonasal sarcoma (BSNS)
- Original name: Low-grade sinonasal sarcoma with neural and myogenic features (LGSSNMF)

Definitions

- Low-grade spindle cell neoplasm of sinonasal tract associated with respiratory epithelium and showing S100 protein and actin reactivity

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare; although, probably under reported
- Age
 - Range: 24-85 years; mean: 52 years
- Sex
 - Female > males (3:1)

Site

- Multiple sites affected, often with extension into orbit (25%) or through cribriform plate (11%)
 - Superior nasal cavity and ethmoid sinus most common

Presentation

- Nonspecific, including difficulty breathing, facial pressure, congestion, pain, and mild epiphora
- Concurrent benign polyps may be seen
- No reported association with neurofibromatosis type 1

Treatment

- Surgery, often accompanied by radiation

Prognosis

- Local recurrences common (44%), between 1-9 years after presentation
- No reported regional or distant metastases
- No patient has yet been reported to die of disease

MICROSCOPIC

Histologic Features

- Infiltrative, highly cellular spindled cell proliferation
 - Poorly circumscribed and unencapsulated
 - Bone invasion may be seen (21%)
- Medium to long fascicles, with herringbone pattern
- Highly uniform cells with elongate nuclei; focally wavy
- Mitoses are rare
- Delicate strands of intercellular collagen without ropy or dense deposition
- Concurrent surface-type respiratory epithelial proliferation invaginated from surface or in small cystic spaces within proliferation
 - Glandular structures intimately associated with spindled cells in several areas
- Focal areas of hemangiopericytoma-like vascularity
- Scattered lymphocytes throughout tumors
- Necrosis, ulceration, and hemorrhage are inconspicuous
- Rhabdomyoblastic differentiation may be seen: Large cells with eosinophilic cytoplasm and focal cross striations

ANCILLARY TESTS

Immunohistochemistry

- S100 protein: Focal, patchy to diffuse in all tumors
- SMA or MSA seen in nearly all tumors, but strong and diffuse reaction with SMA seen in only ~ 50% of cases
- **Focal positive:** CD34, desmin, EMA (weak), AE1/AE3
- **Negative:** SOX10, Myogenin, ER, PR

Genetic Testing

- t(2;4)(q35;q31.1): *PAX3-MAML3* fusion protein
 - Rarely, *PAX3-NCOA1* (inv[2](q35p23))
- Negative *SS18-SSX1* or *SSX2*

DIFFERENTIAL DIAGNOSIS

Fibrosarcoma

- Can be very similar; although, fascicles and herringbone pattern tend to be longer and more well developed
- Collagen deposition more well developed and coarse
- **Positive:** Focal SMA may be seen; concurrent SMA/MSA and S100 protein not seen

Synovial Sarcoma

- Monophasic or biphasic tumors may show similar histologic features as this tumor
- FISH or RT-PCR would show characteristic translocation (*SS18-SSX1* or *SSX2*)

Malignant Peripheral Nerve Sheath Tumor, Including Triton Tumor

- Distinctive alternating light & dark cellular areas; association with peripheral nerves; often seen in NF1; usually high-grade tumors with pleomorphism, necrosis, and ↑ mitoses
- **Positive:** S100 protein, SOX10; **negative:** SMA, MSA

Leiomyosarcoma

- Fascicular architecture, with cigar-shaped nuclei showing blunt ends, perinuclear halos, and eosinophilic cytoplasm
- **Negative:** S100 protein; **positive:** Stronger desmin reaction than BSNS

Mucosal Melanoma

- Spindle cell melanoma with pleomorphism, intranuclear inclusions and prominent nucleoli
- **Positive:** S100 protein, SOX10, HMB45, Melan-A, tyrosinase; **negative:** SMA, MSA

Glomangiopericytoma

- Haphazard architecture of ovoid to spindled cells, with open vascular pattern, peritheliomatous hyalinization, and extravasated erythrocytes
- **Positive:** Nuclear β-catenin, SMA; **negative:** CD34, Bcl-2, S100 protein, SOX10

Solitary Fibrous Tumor

- Spindle cell neoplasm with keloid-like collagen and rich vascularity
- **Positive:** STAT6 (nuclear), CD34, Bcl-2; **negative:** S100 protein, SMA, MSA

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NUT Midline Carcinoma

KEY FACTS

TERMINOLOGY

- *NUT* midline carcinoma
 - Poorly differentiated subset of squamous cell carcinoma (SCC) genetically defined by rearrangement of *NUT* gene

CLINICAL ISSUES

- Peak in young adults, but wide age range (0-78 years)
- ~ 35% affect neck and neck (other sites more commonly)
- Many are midline, but not required
- Rapid clinical onset of symptoms (mass)
- Local control by complete surgical resection and radiation are primary therapies
- Molecular targeted therapies show promise
- Poor prognosis: 6.7-month median survival

MICROSCOPIC

- Poorly differentiated SCC
 - Small to medium-sized cells, round to ovoid nuclei with clear to pale cytoplasm

- Conspicuously monotonous without significant pleomorphism
- Focal, abrupt squamous differentiation
- Tumor necrosis can be seen

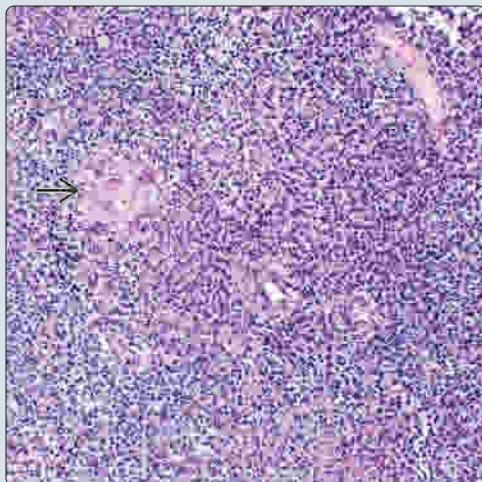
ANCILLARY TESTS

- NUTM1 by immunohistochemistry shows strong, diffuse, speckled nuclear positive
- CK5/6, CK-PAN, p63 are positive in neoplastic cells
- *BRD4-NUTM1* fusion: Majority rearrangement (66%)
 - t(15;19)(q14;p13.1)

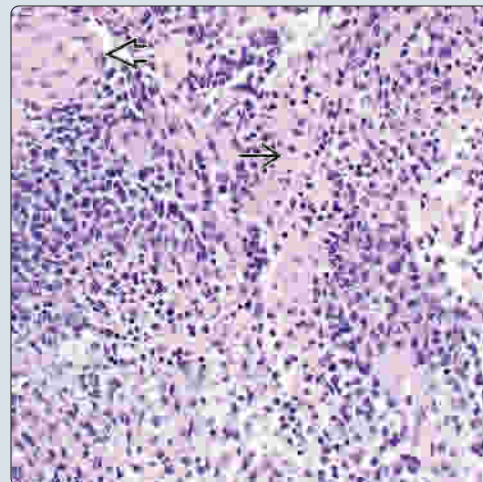
TOP DIFFERENTIAL DIAGNOSES

- SCC
- Neuroendocrine carcinoma
- Sinonasal undifferentiated carcinoma
- Ewing sarcoma

Abrupt Squamous Differentiation

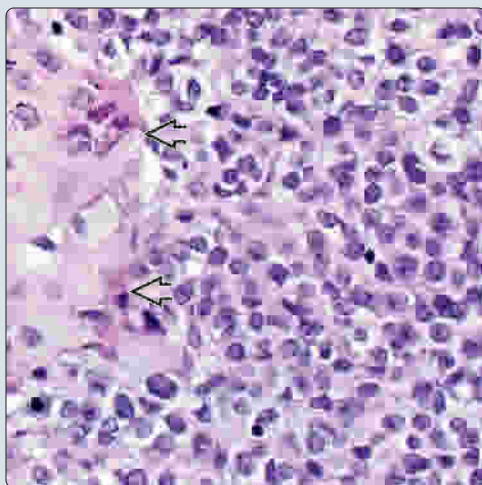


Necrosis and Keratin Pearl

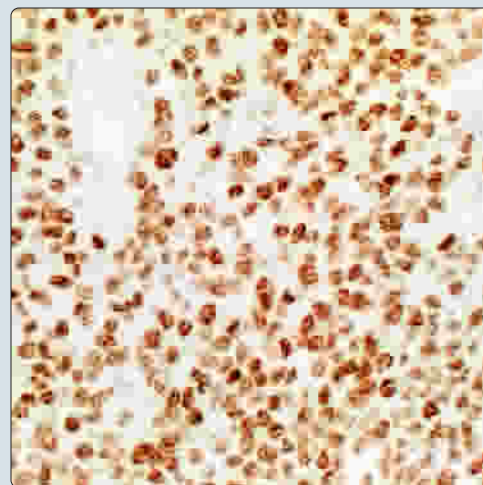


(Left) Poorly differentiated malignant neoplasm arranged in a sheet-like distribution is shown. The cells are monotonous. Note the single island of abrupt squamous differentiation [green arrow]. (Right) The tumor shows a monotonous, undifferentiated morphology. Areas of necrosis [black arrow] are noted. There is also an island of abrupt squamous differentiation [green arrow].

Abrupt Mature Keratinization



NUT Immunohistochemistry



(Left) The neoplastic cells are monotonous with round to ovoid nuclei and clear cytoplasm. Note the area of abrupt mature keratinization [green arrow] that is so characteristic of this tumor type. (Right) NUT antibody shows a strong and diffuse, speckled pattern of nuclear reaction in nearly all of the tumor cells. This IHC confirms the diagnosis. Specific FISH or RT-PCR studies are required to know the translocation partner.

TERMINOLOGY

Abbreviations

- Nuclear protein in testis (NUT)
- *NUT* midline carcinoma (NMC)

Definitions

- Poorly differentiated subset of squamous cell carcinoma (SCC) genetically defined by rearrangement of *NUTM1* gene
 - *NUTM1* gene is on chromosome 15

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Oncogenic mechanism of dual bromodomains and the p300-binding portion of *BRD4-NUTM1* is to sequester p300 to localized regions of chromatin, resulting in global transcriptional repression and blockade of differentiation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare
- Age
 - Peak in young adults, but wide range (0-78 years)
- Sex
 - Equal gender distribution

Site

- ~ 35% affect neck and neck
 - Most cases originally described in mediastinum
- Many are midline, but not required

Presentation

- Rapid clinical onset
- Mass lesion, locally destructive and infiltrative

Treatment

- Surgical approaches
 - Complete surgical resection
- Adjuvant therapy
 - Molecular targeted therapies (bromodomain inhibitors [BETi] and histone deacetylase inhibitors [HDACi]) yield growth arrest
- Local control by complete surgical resection and radiation are primary therapies

Prognosis

- Poor: 6.7-month median survival

MICROSCOPIC

Histologic Features

- Poorly differentiated SCC
- Several features, when present, should prompt additional evaluation for NMC
 - Small to medium-sized cells, round to ovoid nuclei with clear to pale cytoplasm
 - Conspicuously monotonous without significant pleomorphism
 - Focal, abrupt squamous differentiation

- Stratification and gradual differentiation are absent, and it resembles a Hassell corpuscle (thymus)

- Tumor necrosis can be seen

ANCILLARY TESTS

Immunohistochemistry

- NUT shows strong, diffuse, speckled nuclear positive
- CK5/6, CK-PAN, p63 are positive in neoplastic cells
- CD34 is often positive

In Situ Hybridization

- FISH: Used to characterize the *NUT*-fusion (*BRD4-NUTM1* or *NUT*-variant)
- *BRD4-NUTM1* fusion: Majority rearrangement (66%)
 - t(15;19)(q14;p13.1)
 - Very strong association with head and neck tumors
- *BRD3-NUT* or *NUT*-variant fusions make up minority

PCR

- RT-PCR to characterize fusion gene (*BRD4-NUTM1*, *BRD3-NUTM1* or *NUT*-variant) aids in therapy

DIFFERENTIAL DIAGNOSIS

Squamous Cell Carcinoma

- Tends to show more pleomorphism, less monotony, and does not usually show abrupt keratinization or squamous differentiation

Neuroendocrine Carcinoma

- Poorly differentiated histology, but with neuroendocrine chromatin distribution, high mitotic rate, and tends to lack squamous differentiation
- Epithelial and neuroendocrine markers will be positive

Sinonasal Undifferentiated Carcinoma

- Locally destructive, lacks any areas of squamous or glandular differentiation, still shows strong epithelial markers

Ewing Sarcoma

- Similar cellular monotony, but will be positive with CD99, FLI1, and show an *EWSR1* translocation

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Abrupt squamous differentiation in monotonous tumor population

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2. Fang W et al: Clinicopathological significance of NUT rearrangements in poorly differentiated malignant tumors of the upper respiratory tract. *Int J Surg Pathol.* 21(2):102-10, 2013
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HPV-Related Carcinoma With Adenoid Cystic-Like Features

KEY FACTS

TERMINOLOGY

- Sinonasal carcinoma with morphologic features suggestive of adenoid cystic carcinoma
 - Immunohistochemical evidence of myoepithelial differentiation but with features distinctly unusual for adenoid cystic carcinoma, including
 - Presence of surface intraepithelial dysplasia, absence of *MYB* gene rearrangement, and association with human papillomavirus (HPV)

CLINICAL ISSUES


- Sites of occurrence include nasal cavity &/or paranasal sinuses, including ethmoid > maxillary &/or sphenoid; orbital involvement may occur
- Treatment options include surgical resection alone, surgery plus postoperative radiotherapy, or combined chemoradiation therapy
- To date, most patients are alive without evidence of disease or with local recurrence (median: 15 months)

MICROSCOPIC

- Invasive hypercellular lesion with solid, lobular, and nested growth separated by fibrous stroma
- Cribriform and microcystic growth, as well as true ductal structures present
- Neoplastic infiltrate predominantly composed of basaloid cells and true duct cells representing minor component
- Intraepithelial dysplasia of surface epithelium present in majority of cases

ANCILLARY TESTS

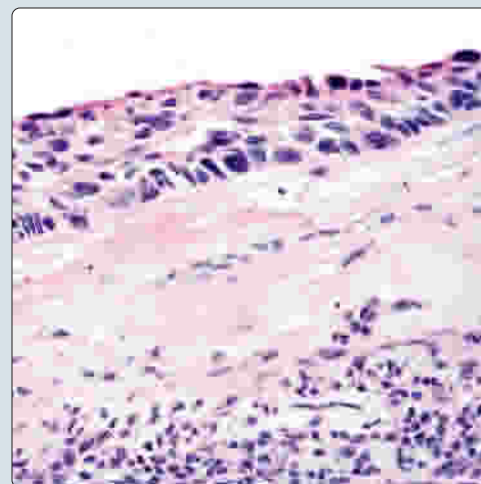
- Cytokeratin (AE1/AE3) positive in all cases
- Basaloid cells express (usually strong and diffuse) 1 or more myoepithelial related markers including p63, calponin, S100 protein, &/or actin
- CD117 (C-kit) consistently reactive
- Strong and diffuse p16 reactivity
- HPV DNA in situ hybridization present
- Absence of *MYB* gene rearrangement


(Left) Sinonasal invasive hypercellular lesion shows cribriform growth reminiscent of the growth pattern seen in adenoid cystic carcinoma. Additional growth patterns that can be seen include solid, lobular, and nested growth separated by fibrous stroma (not shown). The tumor invades through bone . **(Right)** Intraepithelial dysplasia of the surface epithelium is present in these carcinomas, representing a finding that is not identified in adenoid cystic carcinomas.

Cribriform Pattern

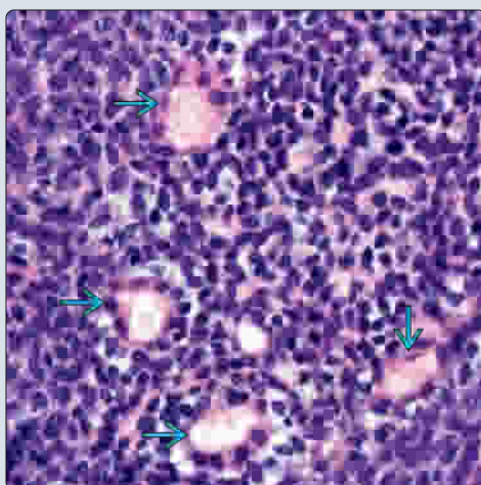


Intraepithelial Dysplasia

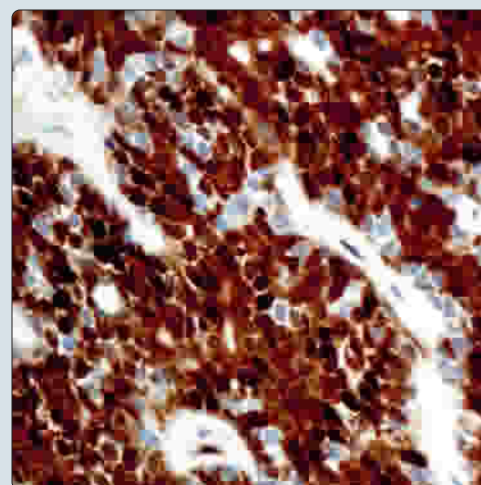


(Left) The neoplastic cells include a predominant basaloid cell population characterized by hyperchromatic and angulated nuclei, scant cytoplasm as well as true ducts comprised of cuboidal cells with eosinophilic cytoplasm . Although not shown, nuclear pleomorphism and increased mitotic activity may be present. **(Right)** Strong and diffuse p16 reactivity is present. Molecular (PCR) confirmation for the presence of human papillomavirus is present in a majority of cases.

Basaloid Cells With Ducts



Strong p16 Reaction



TERMINOLOGY

Abbreviations

- Adenoid cystic (AdC)

Definitions

- Sinonasal carcinoma with morphologic features suggestive of AdC carcinoma
 - Immunohistochemical evidence of myoepithelial differentiation but with features distinctly unusual for AdC carcinoma, including
 - Presence of surface intraepithelial dysplasia, absence of *MYB* gene rearrangement, and association with human papillomavirus (HPV)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare tumor
- Age
 - Wide range: 40-73 years
 - Mean: 55 years
- Sex
 - More common in women than in men

Site

- Sites of occurrence include nasal cavity &/or paranasal sinuses, including ethmoid > maxillary &/or sphenoid; orbital involvement may occur

Presentation

- Presenting symptoms include nasal obstruction and epistaxis; less commonly, epiphora may occur

Treatment

- Options, risks, complications
 - Treatment options include surgical resection alone, surgery plus postoperative radiotherapy, or combined chemoradiation therapy

Prognosis

- Given absence of long-term follow-up, true biologic nature of this neoplasm is yet to be determined
 - In cases identified in literature, albeit with limited follow-up periods (median: 15 months), most patients were alive without evidence of disease or with local recurrence

MACROSCOPIC

Size

- 1 cm to > 5.4 cm
 - Mean: 3 cm

MICROSCOPIC

Histologic Features

- Invasive hypercellular lesion with solid, lobular, and nested growth separated by fibrous stroma
- Cribriform and microcystic growth, as well as true ductal structures present
 - Microcystic spaces filled with basophilic material
 - Ductal structures represent minor component
- Neoplastic infiltrate includes 2 cells types

- Basaloid cells predominate, characterized by hyperchromatic and angulated nuclei, scant cytoplasm, and increased nuclear:cytoplasmic ratio with marked increase in mitotic activity
- True duct cells appear cuboidal with eosinophilic cytoplasm often located at center of lobules surrounded by zones of basaloid cells
- Intraepithelial dysplasia of surface epithelium present in majority of cases
- Tumor necrosis and perineural invasion may be present but lymph-vascular invasion not reported
- Invasive component lacks squamous differentiation

ANCILLARY TESTS

Immunohistochemistry

- Cytokeratin (AE1/AE3) positive in all cases
 - Strong in duct cells; relatively weaker in basaloid cells
- Basaloid cells express (usually strong and diffuse) 1 or more myoepithelial-related markers, including p63, calponin, S100 protein, &/or actin
- CD117 (C-kit) consistently reactive
 - Usually limited to ductal cells but occasionally may be diffuse
- Strong and diffuse p16 reactivity

In Situ Hybridization

- HPV DNA in situ hybridization present
 - Throughout basaloid cells and ductal cells
 - In surface dysplasia and invasive component

PCR

- Quantitative PCR confirmatory of high-risk HPV
 - HPV 33 > HPV 35

Genetic Testing

- Absence of *MYB* gene rearrangement

DIFFERENTIAL DIAGNOSIS

Adenoid Cystic Carcinoma, Solid Variant

- Not associated with intraepithelial dysplastic component
- Presence of *MYB* gene rearrangement

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2. Wenig BM: Recently described sinonasal tract lesions/neoplasms: considerations for the new world health organization book. *Head Neck Pathol*. 8(1):33-41, 2014
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Sinonasal Renal Cell-Like Adenocarcinoma

KEY FACTS

TERMINOLOGY

- Sinonasal renal cell-like adenocarcinoma (SRCLA)
- Rare sinonasal tract adenocarcinoma, which is histologic mimic of renal cell clear cell carcinoma

CLINICAL ISSUES

- Broad age range (22-78 years)
- Mass and nasal obstruction
- Epistaxis and headache
- Surgical removal (resection or endoscopic removal)
- Adjuvant or primary radiotherapy has been employed
- Good prognosis (although too few cases to predict)

MICROSCOPIC

- Hemorrhagic background with prominent vascularity
- Solid to nested pattern with intervening fibrous septa
- Follicular to glandular structures, but also with solid or papillary pattern

- Uniform, cuboidal to polyhedral cells with abundant clear cytoplasm
- Slightly irregular to shrunken nuclei with coarse chromatin
- Intranuclear holes

ANCILLARY TESTS

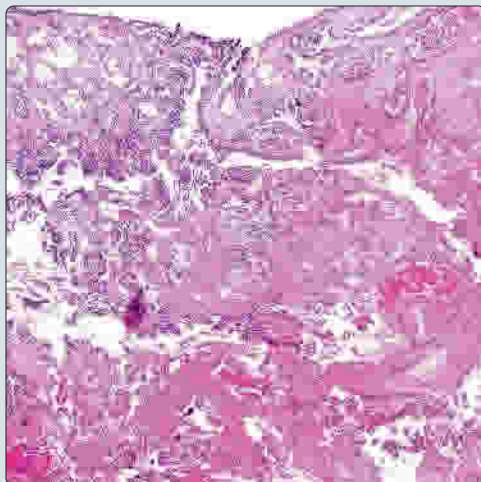
- **Positive:** CK7, CA9
- **Negative:** Vimentin, renal cell carcinoma, thyroglobulin, TTF-1, calponin, pax-8
- **Variable:** CK20, S100 protein, CD10

TOP DIFFERENTIAL DIAGNOSES

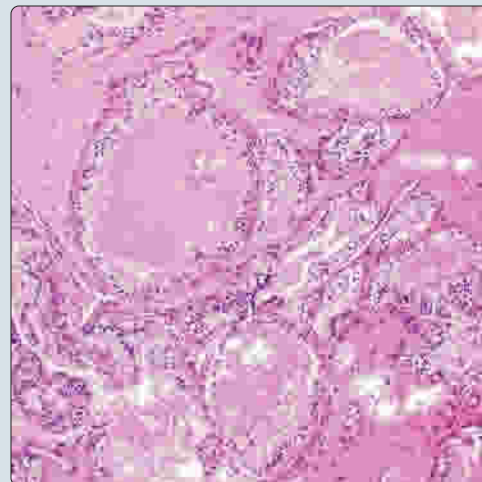
- Metastatic renal cell carcinoma
- Squamous cell carcinoma with clear cell change
- Mucoepidermoid carcinoma (clear cell tumor)
- Metastatic thyroid carcinoma
- Balloon cell melanoma
- Hyalinizing clear cell carcinoma

Renal Cell Carcinoma-Like Growth

(Left) There are several bands of fibrosis noted within this tumor that shows a glandular, follicular and focally papillary architecture. Extravasated blood is noted. **(Right)** The neoplastic cells are arranged in a follicular or glandular architecture. There is a colloid-like secretion. Note the cytoplasmic clearing and very well-defined cell borders. There is limited pleomorphism.

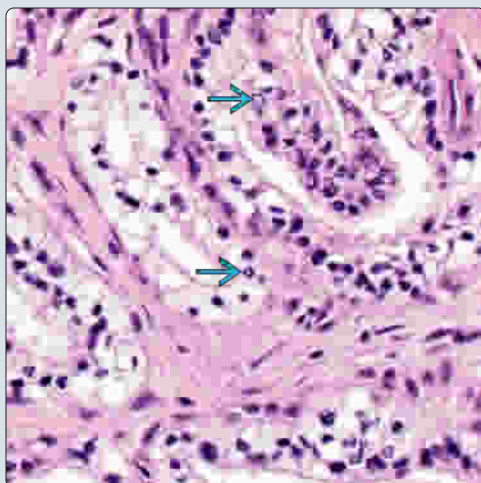


Thyroid-Like Architecture

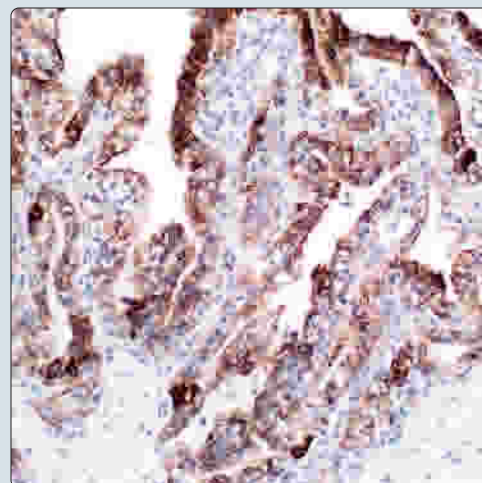


Intranuclear Inclusions

(Left) Clear cytoplasm surrounds round and regular nuclei. There are several intranuclear holes, which are quite unique to this tumor type in this location. **(Right)** The neoplastic cells show a strong and diffuse cytoplasmic and membrane reaction with CK7. The neoplastic cells are also positive with CA9, but negative with pax-8, vimentin, and renal cell carcinoma.



CK7 Immunohistochemistry



TERMINOLOGY

Abbreviations

- Sinonasal renal cell-like adenocarcinoma (SRCLA)

Definitions

- Rare sinonasal tract adenocarcinoma, which is histologic mimic of renal cell clear cell carcinoma
 - von Hippel-Lindau association is unknown

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very rare
- Age
 - Broad range (22-78 years)
- Sex
 - Female > male

Site

- Nasal cavity most common

Presentation

- Mass and nasal obstruction
- Epistaxis and headache
- Rare epiphora and olfactory impairment

Treatment

- Surgical approaches
 - Surgical removal (resection or endoscopic removal)
- Radiation
 - Adjuvant or primary radiotherapy has been employed

Prognosis

- Good (although too few cases to predict)
 - Mean: 6 years
- No metastases or recurrence documented

MACROSCOPIC

General Features

- Polypoid mass and submucosal elevation

MICROSCOPIC

Histologic Features

- Clear cell neoplasm
- Hemorrhagic background with prominent vascularity
 - Extravasated erythrocytes easily seen throughout
- Solid to nested pattern with intervening fibrous septa
- Follicular to glandular structures but also with solid or papillary pattern
 - Inspissated secretions (similar to thyroid colloid)
- Uniform, cuboidal to polyhedral cells with abundant clear cytoplasm
- Low nuclear:cytoplasmic ratio
- Slightly irregular to shrunken nuclei with coarse chromatin
 - Intranuclear holes
- Tumor necrosis is absent
- Mitoses are inconspicuous
- Perineural invasion is not reported

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** CK7, CA9
- **Variable:** CK20, S100 protein, CD10
- **Negative:** Vimentin, RCC, thyroglobulin, TTF-1, calponin, pax-8

DIFFERENTIAL DIAGNOSIS

Metastatic Renal Cell Carcinoma

- Must be excluded clinically &/or radiographically
- Sinonasal tract may be initial presentation of the renal tumor
- SRCLA is positive for CA9, but negative with pax-8, renal cell carcinoma, and vimentin

Squamous Cell Carcinoma With Clear Cell Change

- Squamous differentiation usually identified, with keratinization, intercellular bridges, and infiltrative growth
- Strong reactions with CK5/6 and p63

Mucoepidermoid Carcinoma (Clear Cell Tumor)

- Squamous, transitional and mucous cells
 - Mucicarmine-positive mucocytes
- Strong CK5/6, p63 immunoreactivity is helpful

Metastatic Thyroid Carcinoma

- Colloid-like spaces can mimic metastatic thyroid carcinoma; positive with TTF-1 and thyroglobulin

Balloon Cell Melanoma

- Balloon cells with microvesicular appearance, more pleomorphism, and melanocytic markers

Hyalinizing Clear Cell Carcinoma

- Short tubules, nests, and single cells with strong perineural invasion; lacks follicular or glandular spaces; *EWSR1* translocation

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Must exclude primary renal cell carcinoma, which may have metastasized to sinonasal tract

SELECTED REFERENCES

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5. Stork K et al: Sinonasal renal cell-like adenocarcinoma: a report on four patients. *Head Neck Pathol*. 2(2):75-80, 2008
6. Zur KB et al: Primary description of a new entity, renal cell-like carcinoma of the nasal cavity: van Meegeren in the house of Vermeer. *Arch Otolaryngol Head Neck Surg*. 128(4):441-7, 2002

KEY FACTS

TERMINOLOGY

- Tumors secondarily involving nasal cavity and paranasal sinuses that originate from, but are not in continuity with, primary malignancies of other sites

CLINICAL ISSUES

- < 0.5% of all malignancies of nasal cavity and paranasal sinuses
- Older ages, correlated with increased malignancies of other anatomic sites
- Male > female (3:2)
- Symptoms are identical to primary tumors, and therefore not helpful
- Site
 - Maxillary sinus (33%) > sphenoid sinus (22%), multiple sinuses (22%) > ethmoid sinus (14%) > frontal sinus (9%)
- Metastasis may be 1st manifestation of occult carcinoma
- Surgery is performed for symptomatic relief
- Prognosis is usually grave

MACROSCOPIC

- Polyp can be seen, usually with an intact surface epithelium

MICROSCOPIC

- Metastases to sinonasal tract are hematogenous
 - Look in patulous vessels for tumor thrombi
- Most common tumors are carcinomas (adenocarcinomas)
 - Kidney (40%) > lung (9%) > breast or thyroid (8% each), prostate (7%)

ANCILLARY TESTS

- Prudent and judicious target studies will help with separation from primary tumors
- If known history, select pertinent positive and negative supporting studies

TOP DIFFERENTIAL DIAGNOSES

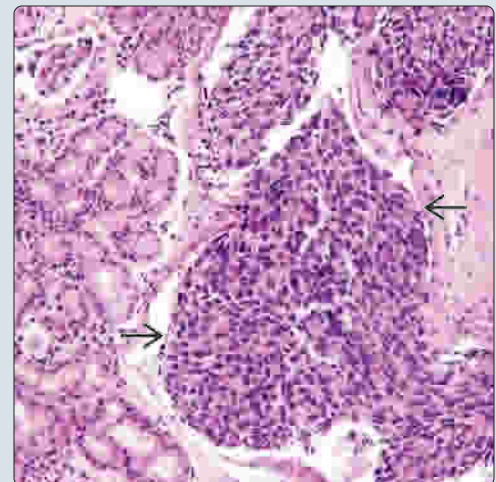
- Primary tumor
- Direction extension

Metastatic Clear Cell Renal Cell Carcinoma

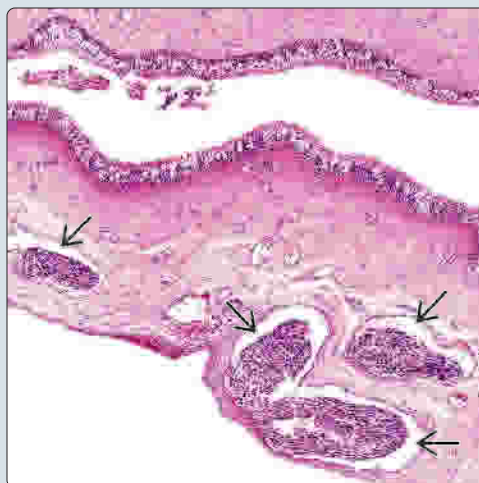


(Left) There is an intact respiratory epithelium overlying a clear cell neoplastic infiltrate. The cell cells are arranged in a vaguely organoid or nested pattern with some extravasated erythrocytes. Appropriate IHC with imaging evaluation can help confirm the diagnosis. **(Right)** The islands of metastatic prostate carcinoma are noted within lymphovascular spaces. The tumor cells are arranged in a glandular to rosette appearance, a mimic of a primary neuroendocrine tumor.

Metastatic Prostate Adenocarcinoma

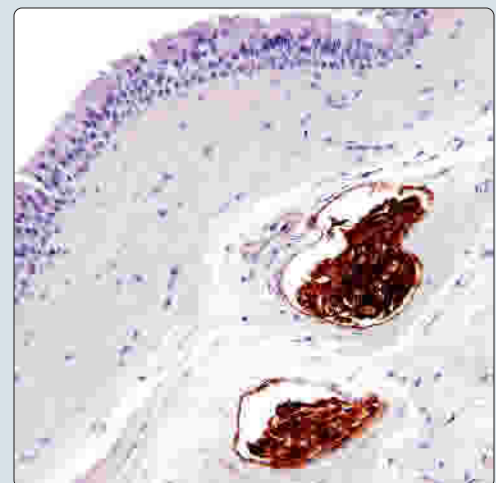


Intravascular Foci of Metastatic Carcinoma



(Left) Metastases frequently occupy dilated vascular spaces. While the type of malignancy is difficult to determine at this power, the intravascular distribution is obvious. This is a metastatic prostate carcinoma. **(Right)** PSA stain helps to confirm the presence of metastatic prostate carcinoma. Some salivary gland tumors can be PSA(+), but a clinical history and intravascular location help separate the diagnoses within the differential considerations.

PSA Highlights Intravascular Tumor Thrombi



TERMINOLOGY

Definitions

- Tumors secondarily involving nasal cavity and paranasal sinuses that originate from, but are not in continuity with, primary malignancies of other sites
 - Lymphomas and leukemias are excluded by definition

CLINICAL ISSUES

Epidemiology

- Incidence
 - < 0.5% of all malignancies of nasal cavity and paranasal sinuses
- Age
 - Older ages; correlated with increased malignancies of other anatomic sites
- Sex
 - Male > female (3:2)

Site

- Maxillary sinus (33%)
- Sphenoid sinus (22%)
- Multiple sinuses (22%)
- Ethmoid sinus (14%)
- Frontal sinus (9%)
- Limited to nasal cavity (10-15%)

Presentation

- Identical to primary tumors and therefore not helpful
- Nasal obstruction
- Epistaxis
 - Especially metastatic renal and thyroid carcinomas
- Headache, facial pain
- Visual disturbances, exophthalmos
- Cranial nerve deficits

Treatment

- Metastasis may be 1st manifestation of occult carcinoma
- Excision is performed for symptomatic relief
 - Rarely, metastatic disease to sinonasal tract may be the only, isolated metastasis (commonly renal cell carcinoma)

Prognosis

- Matches underlying disease but usually part of disseminated disease
- Prognosis is usually grave
 - Also depends on whether sinonasal metastasis is isolated or part of widespread disseminated disease
 - Localized metastasis, treated aggressively, can yield survival of 2-3 years
 - Renal cell carcinoma may be exception, associated with good prognosis with isolated metastatic foci

MACROSCOPIC

General Features

- Metastases may be solitary or multifocal
- Polyp can be seen
- Surface epithelium is usually intact
- Often a subepithelial (submucosal) mass

Size

- Variable; lesions of sinuses often larger than nasal cavity

MICROSCOPIC

Histologic Features

- Metastases to sinonasal tract are hematogenous
 - Look in patulous vessels for tumor thrombi
- Specific tumor type dictates histology
- Most common tumors are carcinomas (adenocarcinomas)
 - Kidney (40%)
 - Lung (9%)
 - Breast (8%)
 - Thyroid (8%)
 - Prostate (7%)
 - Miscellaneous (28%)
- Clear cell primary salivary gland-type tumors may be difficult to separate from metastases
- Melanoma may invade from overlying skin

ANCILLARY TESTS

Immunohistochemistry

- Prudent and judicious target studies will help with separation from primary tumors

DIFFERENTIAL DIAGNOSIS

Primary Tumor

- Primary, poorly differentiated tumors may need to be separated from metastatic tumors
 - Separation can usually be achieved by history, radiographic studies, and immunohistochemistry
 - Salivary gland-type primaries are more common than metastatic tumors

Direct Extension

- Oral cavity primaries (squamous cell carcinoma, melanoma, salivary gland-type adenocarcinomas) may directly extend into nasal cavity or paranasal sinuses
 - Clinical and radiographic evaluation helps
- Gnathic tumors (multiple myeloma, ameloblastoma, odontogenic tumors) may expand into paranasal sinuses and should be considered in differential of an unusual tumor
- Brain (pituitary adenoma, chordoma, meningioma) may extend into these spaces, mimicking primary tumors

SELECTED REFERENCES

1. Terada T: Renal cell carcinoma metastatic to the nasal cavity. *Int J Clin Exp Pathol.* 5(6):588-91, 2012
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5. Kent SE et al: Metastases of malignant disease of the nasal cavity and paranasal sinuses. *J Laryngol Otol.* 98(5):471-4, 1984
6. Bernstein JM et al: Metastatic tumors to the maxilla, nose, and paranasal sinuses. *Laryngoscope.* 76(4):621-50, 1966
7. Friedmann I et al: Metastatic tumours in the ear, nose and throat region. *J Laryngol Otol.* 79:576-91, 1965

PRIMARY TUMOR**Specimen**

- Procedure: Excisional biopsy, resection, including
 - Partial maxillectomy, radical maxillectomy, neck (lymph node) dissection
- Specimen type/tumor site
 - Nasal cavity: Septum; floor; lateral wall; vestibule
 - Paranasal sinus(es): Maxillary, ethmoid, frontal, sphenoid
- Tumor laterality: Left, right, midline
- Tumor focality: Single focus; bilateral; multifocal
- Tumor size: Greatest dimension in centimeters

Histologic Type

- Squamous cell carcinoma (SCC), conventional (keratinizing, nonkeratinizing)
- Variants of SCC
 - Acantholytic SCC, adenosquamous carcinoma, basaloid SCC, papillary SCC, spindle cell SCC, verrucous carcinoma, giant cell carcinoma, lymphoepithelial carcinoma (non-nasopharyngeal), sinonasal undifferentiated carcinoma
- Adenocarcinomas
 - Intestinal type
 - Nonintestinal, non-salivary gland types
 - Salivary gland types
 - Neuroendocrine carcinoma, mucosal melanoma

Histologic Grade

- Well- (G1), moderately (G2), and poorly differentiated (G3)
- Salivary gland carcinomas are separated into low, intermediate, and high grade

Invasion

- Lymph-vascular invasion; perineural invasion
- Margin assessment: Uninvolved or involved by invasive carcinoma or carcinoma in situ [i.e., high-grade (moderate or severe) dysplasia] (include distance in mm and location per orientation)

REGIONAL LYMPH NODES**Cervical Lymph Nodes: Unilateral or Bilateral**

- Separated into pN0 (no regional node metastasis), pN1, pN2(a-c), pN3 based on number & size of involved node(s)
- pN1: Single ipsilateral lymph node ≤ 3 cm
- pN2: Single ipsilateral lymph node > 3 cm but ≤ 6 cm (pN2a) or in multiple ipsilateral lymph nodes < 6 cm (pN2b) or in bilateral or contralateral nodes < 6 cm (pN2c)
- pN3: Metastasis in a lymph node > 6 cm

PROGNOSTIC GROUPS**Maxillary Sinus**

- pT1: Tumor limited to maxillary sinus mucosa with no bone erosion/destruction
- pT2: Tumor causing bone erosion/destruction including extension into hard palate &/or middle nasal meatus
- pT3: Tumor invades bone posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
- pT4: Separated into T4a (moderately advanced local disease) and T4b (very advanced local disease) based on extent of local disease





Nasal Cavity and Ethmoid Sinus

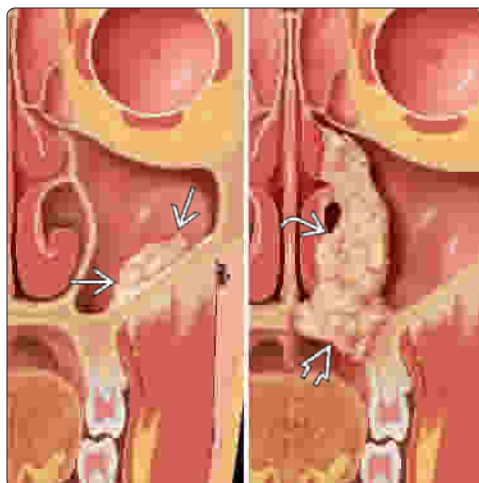
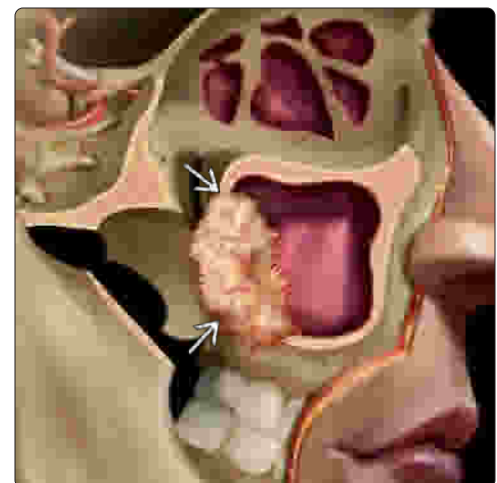
- pT1: Tumor restricted to any 1 subsite \pm bone invasion
- pT2: Tumor invading 2 subsites in single region or extending to adjacent region within nasoethmoidal complex \pm bone invasion
- pT3: Tumor extends to invade medial wall or floor of orbit, maxillary sinus, palate, or cribriform plate
- pT4: Separated into T4a (moderately advanced local disease) and T4b (very advanced local disease) based on extent of local disease

For Mucosal Melanoma

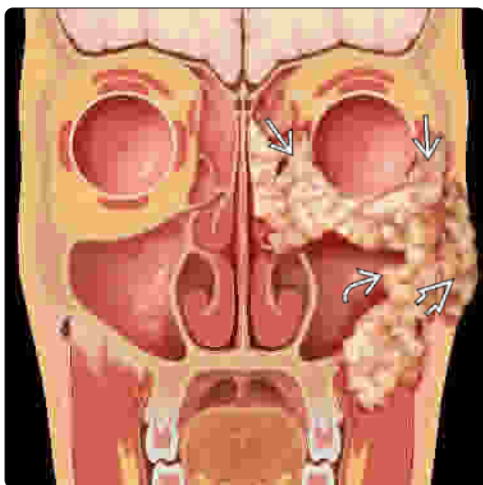
- pT3: Mucosal disease; pT4: T4a (moderately advanced local disease) and T4b (very advanced local disease)
- pN1: Regional lymph node metastases present; pM1: Distant metastasis present

T1 and T2 Maxillary Sinus Carcinoma

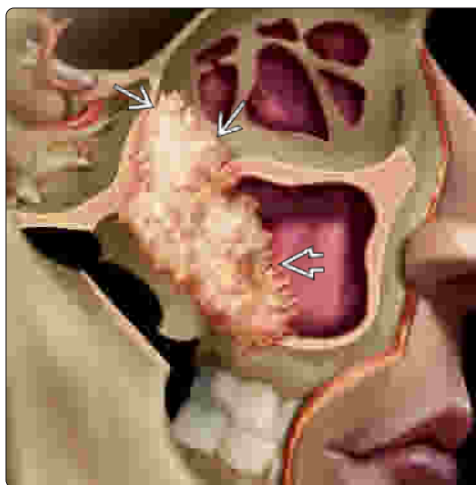
(Left) T1 carcinoma  confined to the maxillary mucosa without bone destruction is shown on the left. On the right, there is a larger tumor that destroys bone and also extends to the hard palate  and middle meatus . Any of these features designate this as a T2 tumor. (Right) T3 maxillary sinus carcinoma invades the posterior bony wall of the maxillary sinus . T3 disease is also determined by invasion of the floor or medial wall of the orbit &/or involvement of the ethmoid sinus, pterygoid fossa, or subcutaneous tissues.






**T3 Maxillary Sinus Carcinoma**

T4a Maxillary Sinus Carcinoma

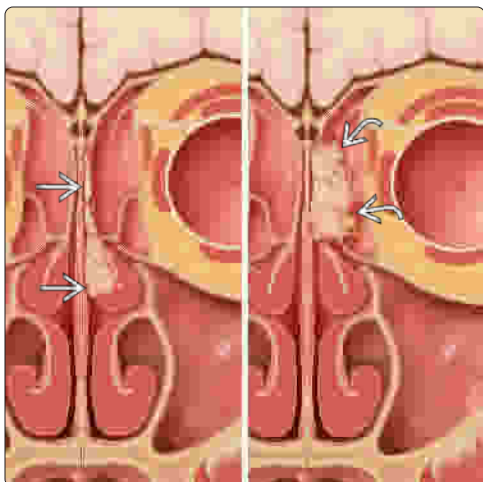


T4b Maxillary Sinus Carcinoma

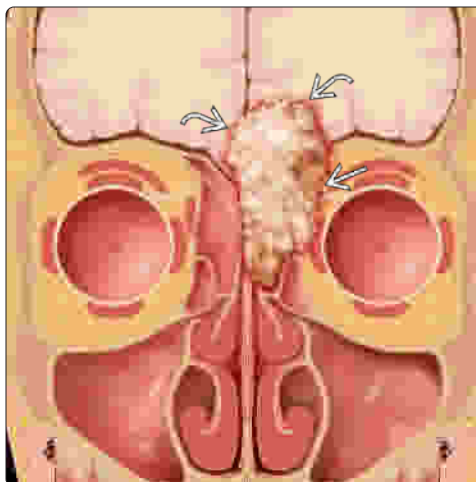






(Left) Moderately advanced maxillary sinus carcinoma  invades the anterior orbit  and extends to the skin of the cheek . T4a disease is also determined by invasion of pterygoid plates, infratemporal fossa, cribriform plate, and sphenoid or frontal sinuses. (Right) Very advanced local maxillary sinus carcinoma  invades the orbital apex . T4b disease is also designated with invasion of dura, brain, middle cranial fossa, nasopharynx, clivus, or cranial nerves other than maxillary division of trigeminal nerve.

T1 and T2 Nasal Cavity Carcinoma

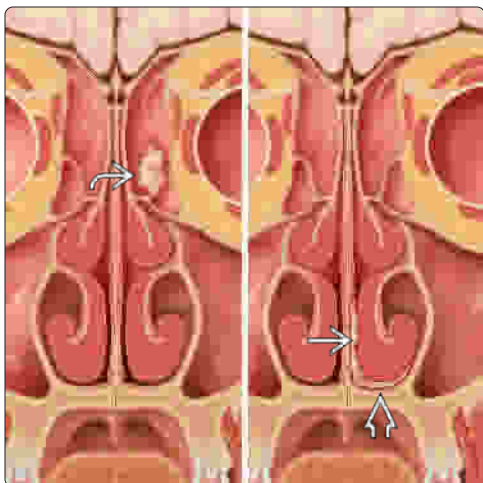


T3 Maxillary Sinus Carcinoma

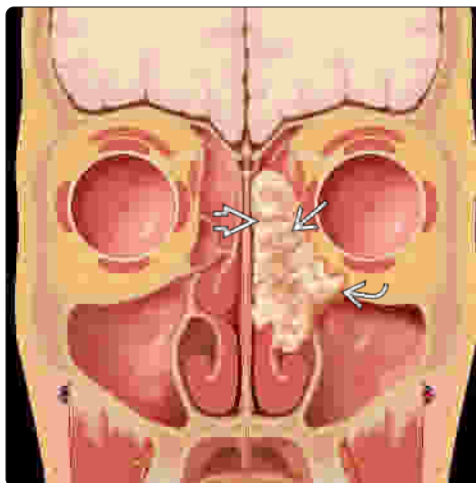








(Left) Coronal graphic (left) demonstrates a small tumor entirely confined to the nasal cavity , which is a T1 tumor and the least common form. On the right, there is extension of tumor from the nasal cavity to the paranasal sinuses , representing a T2 tumor. (Right) Coronal graphic illustrates a T3 nasal cavity carcinoma with extension beyond the nasal cavity and sinuses, into both the orbit  and anterior cranial fossa . T3 tumors extend to invade the medial wall or floor of orbit, maxillary sinus, palate, or cribriform plate.

T1 Ethmoid Sinus Carcinoma and T2 Nasal Cavity Carcinoma



T3 Ethmoid Sinus Carcinoma



(Left) Coronal graphic (left) shows a small tumor confined to the left ethmoid air cells , which is a T1 tumor. On the right, there is a small tumor involving the nasal septum  and nasal floor . Involvement of 2 subsites in the nasal cavity makes this a T2 tumor. (Right) Coronal graphic shows an ethmoid tumor , which extends to the medial orbital wall  and orbital floor . Maxillary sinus, palate, or cribriform plate invasion also constitute T3 disease.

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SECTION 2

Pharynx (Nasal, Oro-, Hypo-)



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MACROSCOPIC ANATOMY

3 Subsites

- Nasopharynx, oropharynx, and hypopharynx are anatomically and functionally distinct

Nasopharynx

- Extends from choanae to superior (nasal) soft palate border
- Includes pharyngeal tonsils and posterolateral walls with eustachian tube openings

Oropharynx

- Extends from superior soft palate border to hyoid bone/valleculae
- Includes palatine tonsils, tonsillar pillars, base of tongue, soft palate, uvula, and posterolateral walls
 - Retromolar trigone is **not** included

Hypopharynx

- Extends from hyoid bone/valleculae to inferior cricoid cartilage border
- Includes pyriform sinuses, postcricoid region, and posterolateral walls

MICROSCOPIC ANATOMY

Nasopharynx

- Lined by ciliated respiratory-type epithelium and stratified squamous epithelium
- Pharyngeal tonsil consists of surface invaginations extending into lymphoid stroma
- Scattered, less prominent lymphoid aggregates can be seen in the non-tonsil mucosa
- Mixed minor mucoserous salivary glands are present in submucosa
- No muscularis mucosa

Oropharynx

- Lined by stratified squamous epithelium
- Palatine tonsils and lingual tonsil (base of tongue) consist of lymphoepithelial crypts extending into lymphoid stroma
 - No basement membrane

- Intimate relationship between epithelium and lymphoid elements
- Keratin debris in lumen is common
- Pure mucous and scattered mixed minor salivary glands are present in submucosa
- No muscularis mucosa

Hypopharynx

- Lined by stratified squamous epithelium
- Pure mucous and scattered mixed minor salivary glands are present in submucosa
- No muscularis mucosa

PITFALLS

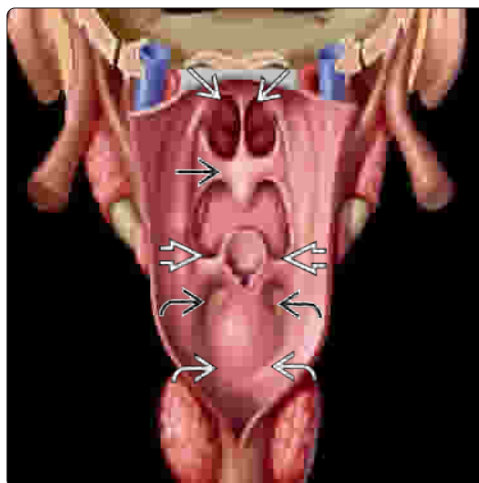
Thornwaldt Cyst

- Epithelium that lines Thornwaldt cyst is identical to respiratory mucosa of nasopharynx
 - Must have radiographic correlation to make definitive diagnosis

Keratin Debris

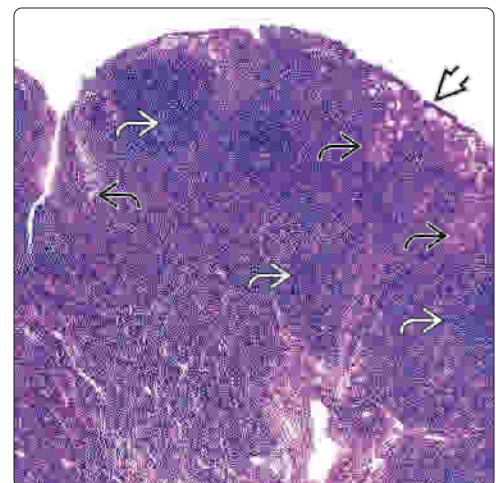
- Keratin debris in oropharynx is not usually part of squamous cell carcinoma (oropharyngeal carcinoma)

Graphic of Pharynx Anatomy

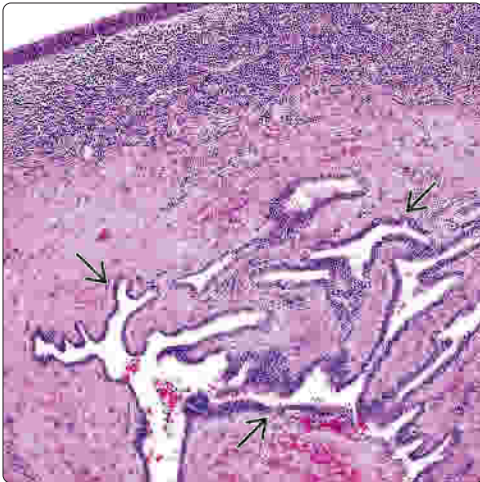


(Left) The nasopharynx extends from the choanae to the superior soft palate. The oropharynx extends from the superior soft palate to the valleculae. The hypopharynx extends from the valleculae to the inferior cricoid cartilage and includes the pyriform sinuses. (Right) The pharyngeal tonsil (adenoid) is lined by ciliated respiratory-type epithelium with elongated mucosal folds extending into lymphoid tissue composed of follicles and interfollicular lymphocytes.

Histology of Pharyngeal Tonsil



Thornwaldt Duct Cyst

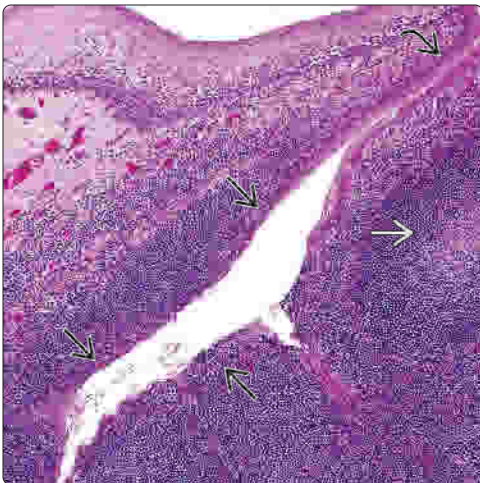


Histology of Oropharyngeal Mucosa

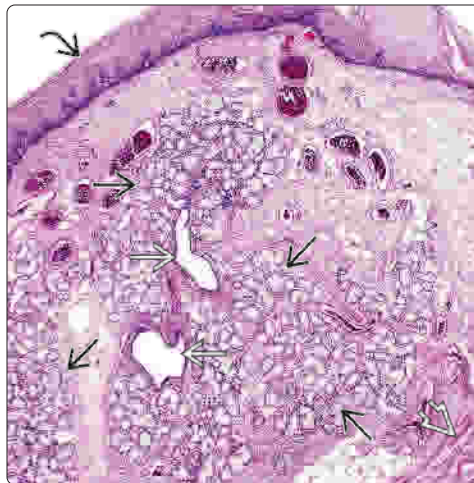


(Left) The developing notochord is in close proximity to the nasopharynx roof. Submucosal notochord remnants can persist and lead to developmental cysts, such as this Thornwaldt duct cyst. Microscopic remnants of the Rathke pouch are also present in the nasopharynx roof of most individuals. (Right) The oropharynx is lined purely by nonkeratinizing stratified squamous epithelium. Scattered submucosal (nontonsillar) lymphoid aggregates are present throughout the oropharynx.

Histology of Tonsil

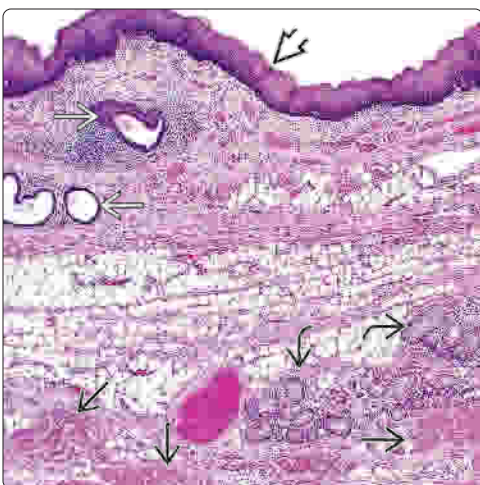


Histology of Normal Uvula



(Left) Palatine and lingual tonsil crypts represent invaginations of the surface squamous epithelium into the lymphoid stroma, which becomes a specialized lymphoepithelium. The stroma is mainly composed of lymphoid aggregates and interfollicular small lymphocytes. (Right) The uvula is lined by stratified squamous epithelium and contains numerous mucous salivary gland lobules with ducts. Thin bundles of skeletal muscle are present in the uvula stroma.

Histology of Hypopharynx



Epithelium of Hypopharynx



(Left) Similar to the oropharynx, the hypopharynx is lined entirely by nonkeratinizing stratified squamous epithelium. Scattered, predominantly mucous, minor salivary gland lobules are present in the submucosa with ducts draining to the surface. Pharyngeal constrictor skeletal muscle is present below the submucosa. (Right) Although the surface typically consists of nonkeratinizing squamous mucosa, exposure to irritants, such as tobacco smoke, can result in surface keratosis.

KEY FACTS

TERMINOLOGY

- Benign, developmental cystic anomaly originating from ectoderm and mesoderm, but not endoderm

CLINICAL ISSUES

- Head & neck is a common site of occurrence
 - Predominantly subcutaneous lesion in head and neck but may occur in other (mucosal) sites
 - Common noncutaneous sites of occurrence
 - Orbit, oral cavity, nasal cavity
- May occur over wide age range but most common in 1st decade of life
- Slow-growing mass lesion not associated with pain
- Simple surgical excision is treatment of choice
- Cured following surgical resection

MICROSCOPIC

- Lined by stratified squamous epithelium with cutaneous adnexal structures in fibroconnective tissue wall

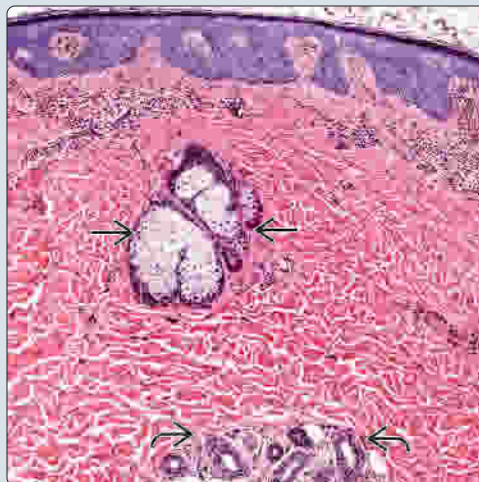
- Adnexal structures may include
 - Hair shafts, sebaceous glands, eccrine glands, apocrine glands
- Cyst content may include keratin or sebaceous material
- May rupture, resulting in florid foreign body giant cell reaction

TOP DIFFERENTIAL DIAGNOSES

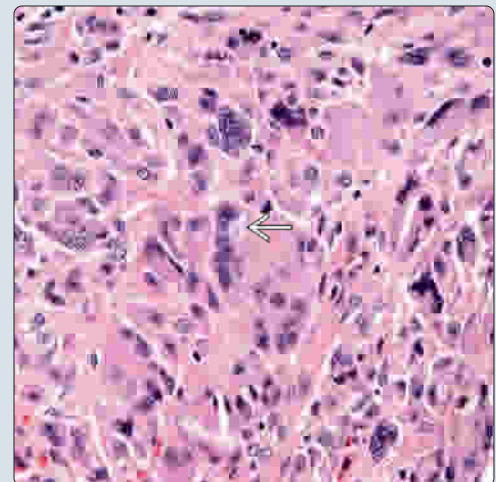
- Teratoma
 - Represent true neoplasm comprised of tissues from all 3 germ layers
- Epidermal inclusion cyst
 - Lined by stratified squamous epithelium with keratin-filled cyst lacking adnexal structures
- Trichilemmal (sebaceous) cyst
 - Lined by stratified squamous epithelium showing trichilemmal keratinization with individual cells increasing in bulk and vertical diameter toward luminal aspect

(Left) A subcutaneous upper neck mass that showed the presence of a cystic lesion lined by stratified keratinizing squamous epithelium with cutaneous adnexal structures in the fibroconnective tissue wall, including sebaceous glands [A] and eccrine glands [B], is shown. **(Right)** Rupture of a dermoid cyst may result in a foreign body giant cell reaction characterized by the presence of histiocytes and multinucleated giant cells, the latter focally with keratin debris [C].

Dermoid Cyst



Ruptured Dermoid Cyst

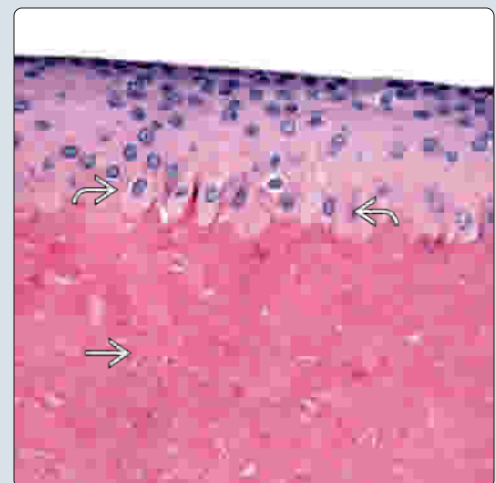


(Left) Epidermal inclusion cysts are lined by keratinizing stratified squamous epithelium, but lack the presence of cutaneous adnexal structures in their fibroconnective tissue walls, a finding that would allow differentiation from a dermoid cyst. **(Right)** The trichilemmal cyst is lined by stratified squamous epithelium with trichilemmal keratinization [A] and abrupt change to keratin in the lumen [B].

Epidermal Inclusion Cyst



Trichilemmal Cyst



TERMINOLOGY

Definitions

- Benign, developmental cystic anomaly originating from ectoderm and mesoderm, but not endoderm

CLINICAL ISSUES

Epidemiology

- Incidence
 - Head & neck
 - Common site of cyst occurrence
 - Accounts for approximately 34% of all dermoid cysts
- Age
 - Most common in 1st decade of life
 - May occur over wide age range
- Sex
 - Equal gender distribution

Site

- Predominantly subcutaneous lesion in head and neck, but may occur in other (mucosal) sites
 - Common noncutaneous sites of occurrence
 - Orbit
 - Oral cavity
 - Nasal cavity
 - Less common sites of occurrence
 - Mandible and maxilla
 - Middle ear
 - Neck (midline or near midline)
 - Upper neck
 - Near thyroid cartilage

Presentation

- Slow-growing mass lesion not associated with pain

Treatment

- Surgical approaches
 - Simple surgical excision is treatment of choice

Prognosis

- Cured following surgical resection

MACROSCOPIC

General Features

- Thin-walled cysts containing gray-white friable material
- Internal aspect of cyst has smooth lining

Size

- Range: A few mm to 12 cm in greatest dimension

MICROSCOPIC

Histologic Features

- Lined by stratified squamous epithelium with cutaneous adnexal structures in fibroconnective tissue wall
 - Adnexal structures may include
 - Hair shafts
 - Sebaceous glands
 - Eccrine glands
 - Apocrine glands
- Cyst content may include keratin or sebaceous material

- May rupture, resulting in florid foreign body giant cell reaction

DIFFERENTIAL DIAGNOSIS

Teratoma

- Represent true neoplasm comprised of tissues from all 3 germ layers

Epidermal Inclusion Cyst

- Lined by stratified squamous epithelium with keratin-filled cyst lacking adnexal structures

Trichilemmal (Sebaceous) Cyst

- Lined by stratified squamous epithelium showing trichilemmal keratinization with individual cells increasing in bulk and vertical diameter toward luminal aspect
 - Occurs without formation of keratohyaline granules
 - Abrupt change from epithelium to eosinophilic keratin in lumen
 - Resembles external root sheath in region of follicular isthmus

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KEY FACTS

TERMINOLOGY

- Cystic tumor located in sellar region filled with fluid, comprised of ciliated epithelium and metaplastic squamous epithelium

ETIOLOGY/PATHOGENESIS

- Abnormal proliferation of Rathke pouch epithelium

CLINICAL ISSUES

- Uncommon in clinical practice but common incidental autopsy finding
- Wide range but peaks in 4th-5th decades
- Female > male (1.3:1)
- Intra- or suprasellar
- Most commonly presents with headache
- Visual impairment (pressure on optic chiasm/apparatus)
- Cysts can be followed radiographically (MR) if asymptomatic and nonenlarging (i.e., incidental lesions)

- Persistent pituitary or visual dysfunction requires management
- Persistence or recurrences develop in ~ 1/3 of patients

MACROSCOPIC

- Cyst contents intraoperatively are clear (CSF-like) to yellow, mucoid to hemorrhagic
- Range: 0.5-4 cm; mean: 2 cm

MICROSCOPIC

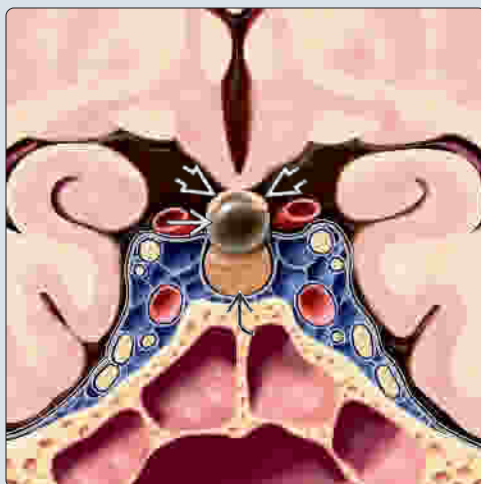
- Cyst filled with mucinous and squamous debris
- Lining of tall, ciliated, pseudostratified columnar epithelium
- Squamous metaplasia and stratified squamous epithelium seen

TOP DIFFERENTIAL DIAGNOSES

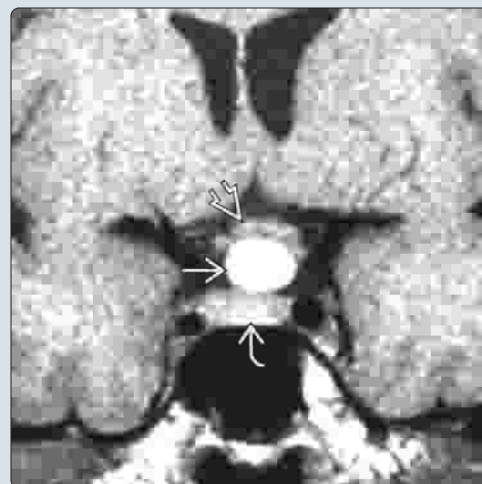
- Craniopharyngioma
- Epidermoid cyst
- Metastatic squamous cell carcinoma

Graphic of Rathke Cleft Cyst

(Left) Coronal graphic shows a typical suprasellar Rathke cleft cyst (RCC) interposed between the pituitary gland and optic chiasm. Note the optic chiasm is bowed upward by cyst mass effect. (Right) Coronal T1 MR shows a classic RCC that elevates and drapes the optic chiasm. The pituitary gland is normal. 50% of RCCs are high signal (bright) on T1 MR imaging, while the other 50% are low signal (dark).

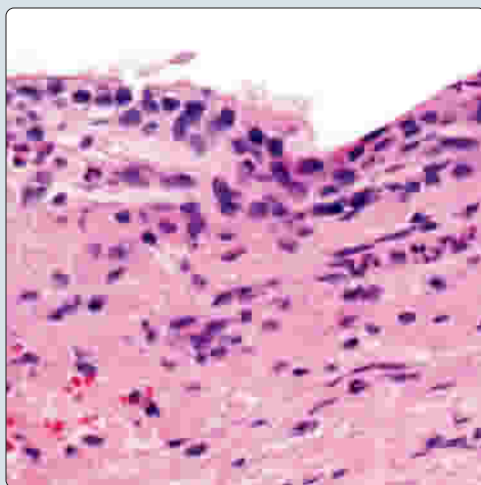


MR With Bright Signal

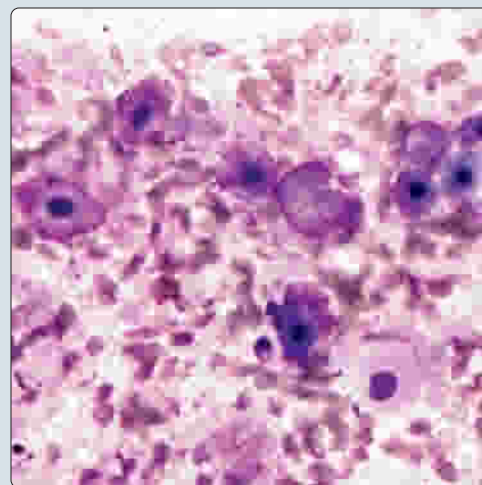


Ciliated Epithelium

(Left) Hematoxylin and eosin shows a ciliated cuboidal to columnar epithelium lining a cystic space. There is fibrosis immediately below. There is no cytologic atypia and pituitary cells are not present. (Right) Nucleated squames are shown in a background of blood. This finding can be seen in an epidermoid cyst, as well as in an RCC. Additional clinical and radiographic correlation would be required.



Nucleated Squames



TERMINOLOGY

Abbreviations

- Rathke cleft cyst (RCC)

Definitions

- Cystic tumor located in sellar region filled with fluid, comprised of ciliated epithelium and metaplastic squamous epithelium

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Abnormal proliferation of Rathke pouch epithelium

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon in clinical practice but common incidental autopsy finding
- Age
 - Wide range but peaks in 4th-5th decades
- Sex
 - Female > male (1.3:1)

Site

- Intra- or suprasellar

Presentation

- Most commonly presents with headache
- Visual impairment (pressure on optic chiasm/apparatus)
- Pituitary/hypothalamic endocrine disturbance frequently identified
 - Hyperprolactinemia, growth hormone excess, amenorrhea; diabetes insipidus can be seen
 - Pituitary apoplexy is rare

Treatment

- Options, risks, complications
 - Cysts can be followed radiographically (MR) if asymptomatic and nonenlarging (i.e., incidental lesions)
 - Persistent pituitary or visual dysfunction requires management
 - Surgical complication includes diabetes insipidus
 - Packing sella may result in predisposition to recurrent cyst formation
- Surgical approaches
 - Transsphenoidal (transnasal) or transcranial sella surgery
- Drugs
 - Instillation of sclerosing agent (absolute alcohol) to treat residual cyst lining

Prognosis

- Persistence or recurrences develop in ~ 1/3 of patients
 - Extent of cyst removal and presence of squamous metaplasia in cyst wall increase likelihood of recurrence
 - Follow-up imaging is recommended for at least 10 years as recurrences may take time to develop

IMAGING

MR Findings

- Variable intensity of cystic material in RCC makes radiographic images overlap with other entities
- Suprasellar or intrasellar mass with ovoid shape, small tumor volume, cystic characteristics, no calcifications, and no or thin cyst wall enhancement are more common in RCC
- Enhancement on MR imaging coincides with displacement of pituitary gland, giving posterior ledge sign
- Cyst wall lacks enhancement with gadolinium

MACROSCOPIC

General Features

- Cyst contents intraoperatively are clear (CSF-like) to yellow, mucoid to hemorrhagic

Size

- Range: 0.5-4 cm; mean: 2 cm

MICROSCOPIC

Histologic Features

- Cyst filled with mucinous and squamous debris
- Lining of tall, ciliated, pseudostratified columnar epithelium
- Squamous metaplasia and stratified squamous epithelium
- Inflammatory cells seen, including acute and chronic cells
- Isolated glands may be seen
- Concurrent pituitary adenoma can be demonstrated

ANCILLARY TESTS

Cytology

- Clinoradiologic features and anatomic site used in conjunction with cytology
- Aspirates show single and aggregates of keratinizing squamous cells, anucleate squames, and hemosiderin-laden macrophages

Immunohistochemistry

- **Positive** with LMW keratins: CK8 and CK20
- **Negative** for nuclear accumulation of β -catenin

DIFFERENTIAL DIAGNOSIS

Craniopharyngioma

- Tends to be larger
- Has calcifications, keratinaceous debris, multinucleated giant cells, basaloid epithelium
- Negative with CK8 and CK20

Epidermoid Cyst

- Pituitary tissue immediately adjacent to squamous epithelium, prominent keratohyaline granules

Metastatic Squamous Cell Carcinoma

- Remarkably atypical epithelial cells, background of necroinflammatory debris

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KEY FACTS

TERMINOLOGY

- Expansion of virtual space in nasopharynx midline into cyst where embryonic notochord and nasopharyngeal ectoderm meet

ETIOLOGY/PATHOGENESIS

- Pharyngeal bursa (Tornwaldt bursa) is persistent communication between roof of nasopharynx and notochord

CLINICAL ISSUES

- Large radiographic study identified in 0.06% of patients
- Peak incidence at 30-55 years
- Posterior-superior nasopharynx midline
- Most cases are asymptomatic, radiographically detected
- Long symptom duration; cyst forms gradually as fluid accumulates following duct obliteration
- Periodic, purulent, foul-tasting discharge of fluid into mouth or postnasal drip

- Ear fullness, earache, ear discomfort (eustachian tube dysfunction)
- Asymptomatic patients can be followed with serial images (stable size) or treated by marsupialization

IMAGING

- MR is exam of choice: High signal intensity on both T1- and T2-weighted images due to protein &/or hemorrhage within cyst

MICROSCOPIC

- Cyst up to 3 cm (mean: 0.6 cm)
- Well-circumscribed rounded cyst immediately deep to mucosa
- Cyst lined by respiratory epithelium
- Fluid with variable proteinaceous and inflammatory debris

TOP DIFFERENTIAL DIAGNOSES

- Nasopharyngeal teratoma, branchial cleft cyst, encephalocele/meningocele

MR of Tornwaldt Cyst

(Left) Sagittal T2WI MR shows a high signal Tornwaldt cyst in the superficial nasopharyngeal soft tissues. The high signal is the result of high protein content in the cyst fluid. (Right) There is a submucosal mass obscuring the Eustachian tube seen in the right nasopharynx. This is an example of a Tornwaldt cyst. (Courtesy D.W. Flis, MD.)

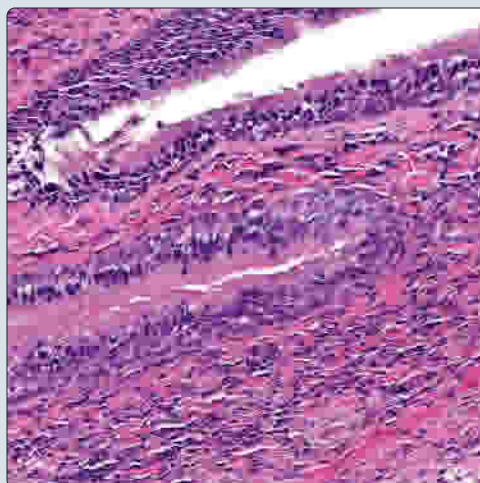


Endoscopic View of Submucosal Mass



Respiratory Epithelial Lining of Cyst

(Left) Hematoxylin and eosin shows a respiratory epithelial-lined cystic cavity. This is a common finding in a Tornwaldt cyst, and it requires a clinical &/or radiographic correlation. (Right) There is a very thin respiratory epithelial lining of this Tornwaldt cyst. There is background debris and fibrous connective tissue.



Simple Cyst



KEY FACTS

TERMINOLOGY

- Severe high-density lipoprotein (HDL) deficiency syndrome characterized by accumulation of cholesterol in tissue macrophages with prevalent atherosclerosis (α -lipoprotein deficiency)

ETIOLOGY/PATHOGENESIS

- Autosomal-recessive inherited disorder
- HDLs play central role in transporting cholesterol from peripheral tissues to liver for elimination
- Caused by mutations in cell membrane protein adenosine triphosphate (ATP)-binding cassette transporter A1 (*ABCA1*) and cholesterol-efflux regulatory protein (CERP) pathways

CLINICAL ISSUES

- Affected families identified on Tangier Island, VA in Chesapeake Bay
- All ages, but usually < 40 years at initial presentation

- Equal gender distribution
- Massive, abnormal accumulation of cholesterol esters in macrophages in many tissues
 - Abnormal accumulation in tonsils, lymph nodes, spleen, liver, and bone marrow
- Peripheral neuropathy
- Atherosclerosis
- Heterozygotes have low concentrations of HDL
- Homozygotes
 - Severe deficiency or absence of HDL-C in plasma
 - LDL levels tend to be reduced

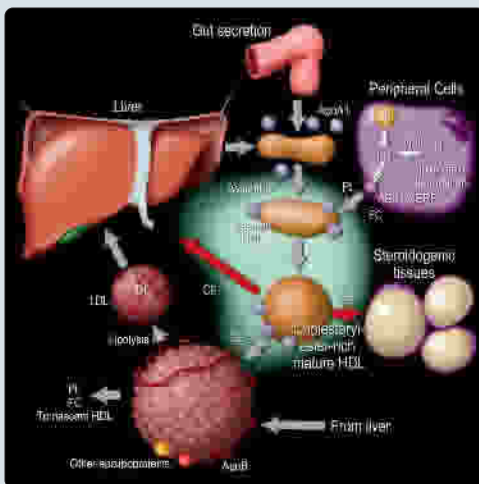
MACROSCOPIC

- Bright orange-yellow tonsils and adenoids (> 4-5 cm)

MICROSCOPIC

- Prominent accumulation of foamy histiocytes (xanthoma cells) in clusters
- In parafollicular or interfollicular zones

Graphic of Phospholipid Pathway



Enlarged Orange Tonsils

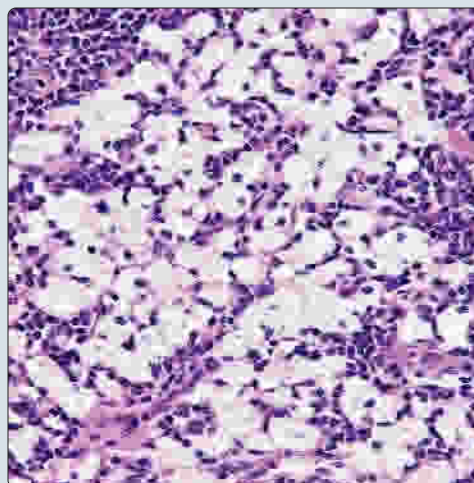


(Left) CERP is necessary for bulk transfer of free cholesterol (FC) and phospholipids out of cells. ApoA1 and HDL act as acceptors for cholesterol. The FC is esterified (cholesteryl ester, CE) and transferred to LDL and to cells by SRB1. TD patients have defects in CERP, with ApoA1 rapidly cleared from the circulation and degraded (defects of TD are light green). (Right) Enlarged tonsils with a slightly orange appearance are shown. (National Library of Medicine: Jiménez Díaz Memorial Lecture, Madrid, 1974.)

Parafollicular Histiocyte Accumulation



Histiocytes With Cleared Cytoplasm



(Left) There is a parafollicular accumulation of pale-staining, foamy histiocytes. These histiocytes contain the lipid material. (Right) Hematoxylin and eosin stained material shows histiocytes filled with clear esters. Organisms are not identified (using other histochemical studies).

KEY FACTS

TERMINOLOGY

- Systemic, benign, self-limiting infectious lymphoproliferative disease primarily caused by, but not limited to, EBV infection

ETIOLOGY/PATHOGENESIS

- EBV estimated to cause 80-95% of infectious mononucleosis cases
 - Strongly tropic for B lymphocytes
 - Also tropic for T lymphocytes
- Virus penetrates nasopharyngeal epithelium and infects B lymphocytes
- EBV-infected B cells proliferate and elicit humoral and cellular immune responses

CLINICAL ISSUES

- Primarily affects adolescents and young adults
- Acute pharyngotonsillitis with patients experiencing sore throat, fever, and malaise

- Absolute lymphocytosis with > 50% lymphocytes in total leukocyte population of > 5,000/mm³
- Prominent atypical lymphocytes (Downey cells) often > 10% of total leukocyte count
- Therapy is supportive, including rest and fluid intake

MICROSCOPIC

- Distortion &/or partial effacement of nodal/tonsillar architecture with reactive follicular hyperplasia characterized by enlarged and irregularly shaped germinal centers
- Expansion of interfollicular areas with polymorphous proliferation of small lymphocytes, transformed lymphocytes, immunoblasts, plasma cells, and Reed-Sternberg-like cells

ANCILLARY TESTS

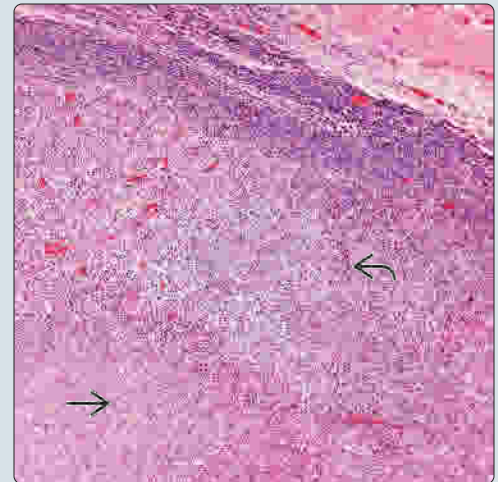
- B-cell (CD20) and T-cell (CD3) reactivity
- Immunoblasts may be CD30(+)
- EBER(+) in proportion of small and large cells

Lymphoid Hyperplasia

(Left) Excised tonsil shows submucosal lymphoid proliferation with distortion and partial effacement of tonsillar architecture, preservation of germinal centers with interfollicular (cellular) expansion and foci of necrosis. The germinal centers are enlarged and irregularly shaped. **(Right)** Diffuse cellular proliferation and an area of confluent necrosis is shown. These findings, in conjunction with the atypical cytomorphology at higher magnification, suggest a diagnosis of a malignant lymphoma.

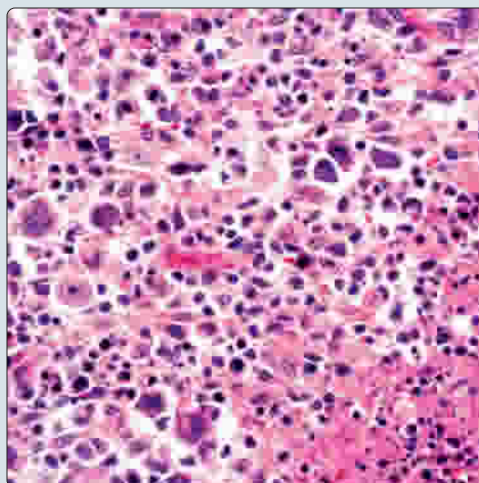


Diffuse Proliferation and Necrosis

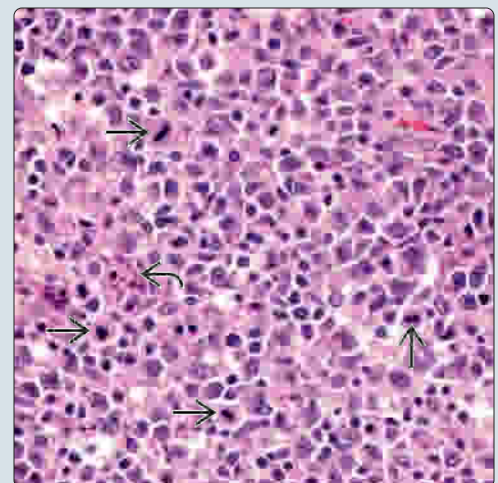


Atypical Interfollicular Proliferation

(Left) At high magnification, the interfollicular cellular proliferation includes cells with marked nuclear atypia, including multinucleated cells, individual cell necrosis, and confluent focus of necrosis (lower right). **(Right)** Diffuse proliferation of polymorphic-appearing cells is shown with nuclear atypia, increased mitotic activity, and individual cell necrosis. The overall light microscopic features are worrisome for a malignant lymphoma, in particular, a diffuse large B-cell lymphoma.



Atypical Interfollicular Proliferation



TERMINOLOGY

Abbreviations

- Infectious mononucleosis (IM)

Definitions

- Systemic, benign, self-limiting infectious lymphoproliferative disease primarily caused by, but not limited to, Epstein-Barr virus (EBV) infection

ETIOLOGY/PATHOGENESIS

Infectious Agents

- EBV estimated to cause 80-95% of IM cases
 - EBV: Enveloped icosahedral herpesvirus with double-stranded linear DNA
 - Strongly tropic for B lymphocytes
 - Also tropic for T lymphocytes
 - Virus penetrates nasopharyngeal epithelium and infects B lymphocytes
 - EBV-infected B cells proliferate and elicit humoral and cellular immune responses
 - Associated with other nonneoplastic lesions, including
 - Oral hairy leukoplakia
 - NK-/T-cell chronic active EBV infection (CAEBV)
 - Post-transplantation lymphoproliferative disease (PTLD)
 - EBV is important pathogen in recipients of solid organ transplants (SOT)
 - EBV disease and its associated PTLD more frequently seen when primary EBV infection occurs after transplant, common scenario in pediatric SOT recipients
 - Possible role for EBV suggested in chronic inflammatory/autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis
 - Associated with neoplasms, including
 - Epithelial neoplasms
 - Nasopharyngeal-type nonkeratinizing carcinomas (differentiated and undifferentiated)
 - Lymphoepithelial-like carcinoma (e.g., salivary gland, others)
 - Gastric carcinoma
 - Hematolymphoid neoplasms
 - NK-/T-cell lymphoma, nasal type
 - Burkitt lymphoma (occurs in ~ 30-40% of sporadic cases)
 - Central nervous system lymphoma
 - Lymphomatoid granulomatosis
 - Aggressive NK-cell leukemia/lymphoma
 - T-cell lymphoproliferative disorders of childhood
 - EBV positive diffuse large B-cell lymphomas of elderly
 - Diffuse large B-cell lymphoma associated with chronic inflammation (pyothorax-associated lymphoma)
 - Angioimmunoblastic T-cell lymphoma
 - AIDS-related lymphomas
 - Primary effusion lymphoma
 - Sarcoma

- Leiomyosarcoma

- Other microorganisms associated with mononucleosis-like syndromes include
 - Cytomegalovirus (CMV)
 - *Toxoplasma gondii*
 - Rubella
 - Hepatitis A virus
 - Adenoviruses

CLINICAL ISSUES

Epidemiology

- Age
 - May occur in all age groups, but primarily affects adolescents and young adults
- Sex
 - Equal gender distribution

Site

- Tonsils

Presentation

- Acute pharyngotonsillitis with patients experiencing sore throat, fever, and malaise
 - Pharyngotonsillitis often severe and may be exudative
 - Pharyngitis characterized by marked swollen and enlarged tonsils covered by dirty gray exudates
- Lymphadenopathy and hepatosplenomegaly with chemical evidence of hepatitis may represent systemic manifestations of disease
 - Lymphadenopathy commonly of posterior cervical lymph nodes, but may involve anterior and posterior nodes
 - Tender lymphadenopathy
- Prodromal period of 2-5 days with malaise and fatigue frequently occurs prior to onset of full syndrome

Laboratory Tests

- Absolute lymphocytosis with > 50% lymphocytes in total leukocyte population of > 5,000/mm³
- Prominent atypical lymphocytes (Downey cells) often > 10% of total leukocyte count
 - Atypical lymphocytes in peripheral blood thought to represent mostly activated T-lymphocyte populations in response to B-cell infection
- Mild to moderate elevations of liver enzymes, including aspartate and alanine aminotransferase
- Diagnosis confirmed by demonstration of serum antibodies to
 - Horse red cells (positive monospot test)
 - Sheep erythrocytes (positive Paul-Bunnell heterophile antibody test)
- Non-EBV infectious agents causing IM not associated with positive heterophile antibody test and monospot test
- Patients consistently heterophile antibody or monospot negative; serodiagnosis is invaluable and includes
 - Appreciable serum response to EBV viral capsid antigen (VCA) with both IgM and IgG antibodies at time of clinical presentation
 - IgM antibodies to VCA disappear within 2-3 months following infection
 - IgG antibodies to VCA persist for life, indicative of chronic carrier state

- At presentation or shortly thereafter, many patients develop antibodies to early antigen complex (EA)
 - Antibodies to EA disappear within 2-6 months following infection
- During early phase of primary infection, antibodies to EBV nuclear antigens (EBNA) are usually not demonstrable
 - Anti-EBNA antibodies persist for life, indicative of chronic carrier state

Treatment

- Options, risks, complications
 - Therapy is supportive, including rest and fluid intake

Prognosis

- Favorable clinical course, often with resolution of symptoms over period of several months
- Rarely, serious and potentially fatal complications may develop and include
 - Airway obstruction and splenic rupture, latter secondary to splenic involvement with massive splenomegaly
 - Most serious complications arise in individuals with X-linked lymphoproliferative disease (XLP)
 - XLP caused by mutations in *SH2D1A* and *XIAP (BIRC4)*; may also occur rarely with no identified underlying genetic cause
 - Patients are immunosuppressed and possess rare, familial, fatal form of combined immunodeficiency
 - 3 most commonly recognized phenotypes of *SH2D1A*-related XLP
 - Hemophagocytic lymphohistiocytosis (HLH) associated with EBV infection
 - Dysgammaglobulinemia
 - Malignant lymphomas: Typically high-grade B-cell lymphomas, non-Hodgkin type, often extranodal, and in particular involve intestine

MICROSCOPIC

Histologic Features

- Distortion &/or partial effacement of nodal/tonsillar architecture with reactive follicular hyperplasia
 - Characterized by enlarged and irregularly shaped germinal centers
- Expansion of interfollicular areas with polymorphous proliferation of
 - Small lymphocytes, transformed lymphocytes, immunoblasts, plasma cells, Reed-Sternberg-like cells
 - Presence of immunoblasts may result in mottled appearance
- Lymphocytic and immunoblastic proliferations often display marked cytologic atypia with
 - 1 or more prominent nucleoli, increased mitotic activity, phagocytosis
- Immunoblasts may
 - Cluster or form sheets effacing portions of tissue, simulating malignant lymphoma
 - Occasionally be binucleate, simulating appearance of Reed-Sternberg cells of Hodgkin lymphoma
- Necrosis may be seen
 - Usually focal and characterized by individual cell necrosis, although larger confluent zones may be present

- Vascular proliferation with prominent endothelial cells always present

ANCILLARY TESTS

Histochemistry

- Stains for microorganisms are negative

Immunohistochemistry

- B-cell (CD20) and T-cell (CD3) reactivity without immunoreactivity for CD15 (Leu M1)
- Immunoblasts may be CD30(+)
- Immunoreactivity can be seen for
 - EBV latent membrane protein
 - EBER(+) in proportion of small and large cells

Genetic Testing

- PCR analysis detects virus
 - Represent more reliable and sensitive means for detecting presence of virus than serodiagnosis
- Absence of gene rearrangements

DIFFERENTIAL DIAGNOSIS

HIV Infection

- Morphologic features of acute and chronic phases of HIV tonsils not present in IM
- Presence of immunoreactivity for HIV p24, absence of EBV

Lymphoma

- Diffuse large cell B-cell lymphoma and anaplastic CD30(+) large cell lymphoma
 - Typically includes effacement of architecture with loss of germinal centers
 - Monoclonality by immunohistochemistry
 - Presence of gene rearrangements

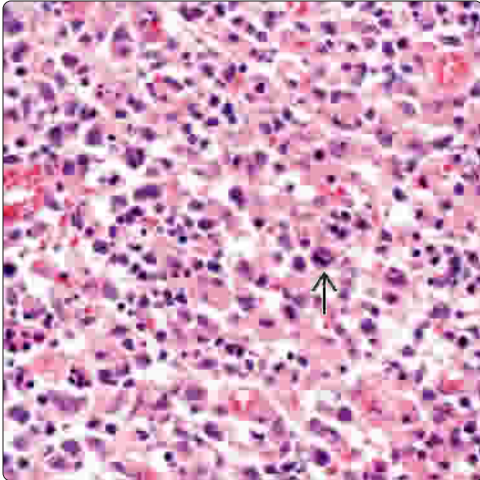
Hodgkin Lymphoma

- Primary Hodgkin lymphoma of tonsils &/or mucosal sites of upper aerodigestive tract exceedingly rare

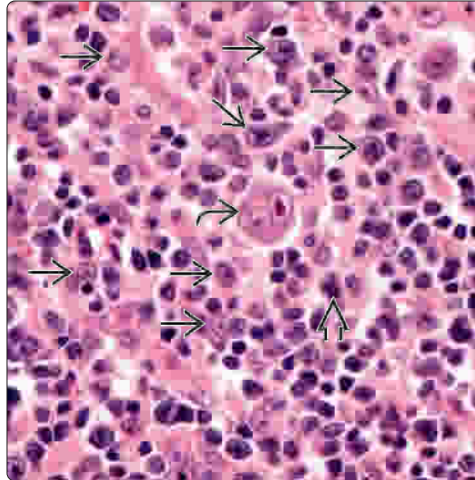
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Atypical Interfollicular Proliferation

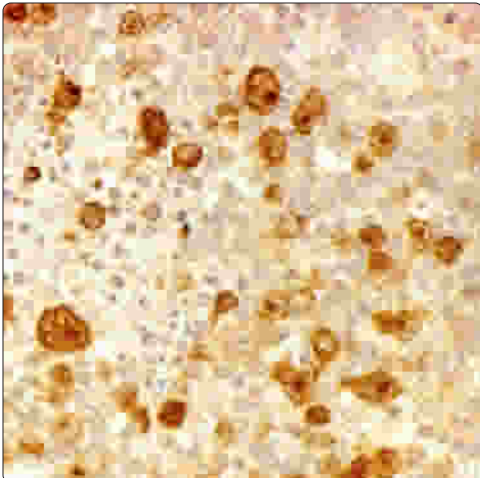


Reed-Sternberg-Like Cells

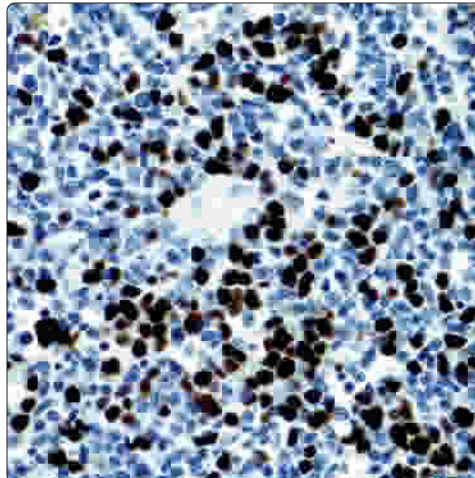


(Left) Interfollicular proliferation of a markedly atypical cellular proliferation is shown with individual cell necrosis and an atypical mitotic figure [X]. (Right) The interfollicular area includes a proliferation of numerous immunoblasts [X], as well as lymphocytes, plasma cells [X], and Reed-Sternberg-like cells [X]. Out of context, at higher magnification these cytomorphic features certainly suggest a possible diagnosis of lymphoma.

EBV-LMP Staining

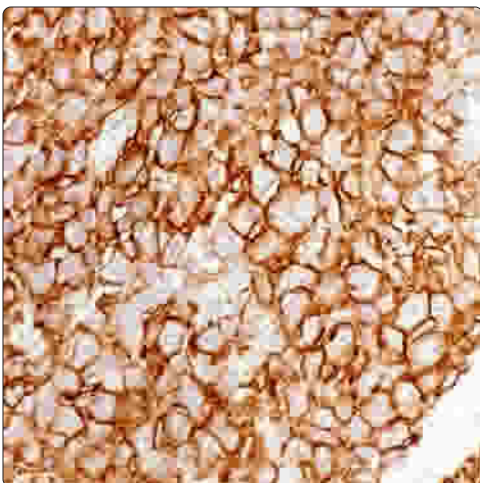


EBER Reactivity

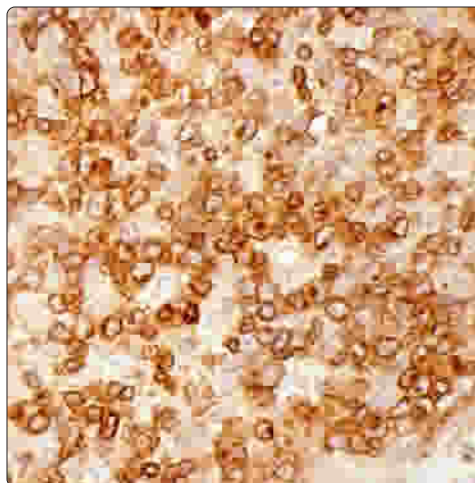


(Left) EBV is the cause in the majority of cases of infectious mononucleosis, as shown by the presence of immunoreactivity for EBV latent membrane protein. (Right) In situ hybridization for EBV-encoded RNA (EBER) is positive in a proportion of cells, including small and large cells (nuclear staining). EBER is more sensitive and specific than EBV latent membrane protein.

B-Cell Marker Immunoreactivity



T-Cell Marker Immunoreactivity



(Left) Immunoreactivity is present for the B-cell marker CD20. (Right) Immunoreactivity for the T-cell marker CD3 is shown. Immunoreactivity for B- and T-cell markers, even in the presence of a markedly atypical cellular proliferation with increased mitotic activity and necrosis, would support a benign lymphoid cell proliferation rather than a lymphoma. A diagnosis of infectious mononucleosis is established in a patient with typical clinical presentations and appropriate laboratory findings.

KEY FACTS

TERMINOLOGY

- Primary HIV infection of tonsils &/or adenoids
 - Occurs in association with known systemic disease
 - May represent initial manifestation of HIV infection in patients not known to be HIV infected

ETIOLOGY/PATHOGENESIS

- HIV-1 belongs to human retrovirus of lentivirus genus
 - Preferentially infects CD4(+) (helper) T-cell lymphocytes
 - Leads to destruction of cellular immunity, leading to immunosuppression, rendering host susceptible to opportunistic infections and tumors, a hallmark of AIDS
- Transmission occurs through blood, sexual contact (bodily fluids), maternofetal routes

CLINICAL ISSUES

- Nasopharyngeal or tonsillar mass usually bilateral but may be unilateral
 - Concurrent cervical adenopathy may be present

- Use of antiretroviral chemotherapy may significantly prolong life and disease-free interval
- Occurs most frequently in 3rd-5th decades (median age: 4th decade); male > female

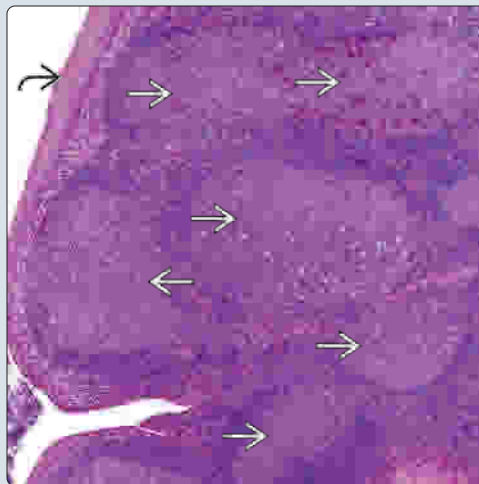
MICROSCOPIC

- Acute &/or chronic stage
 - Florid follicular hyperplasia, follicle lysis with areas of follicular involution
 - Multinucleated giant cells cluster adjacent to &/or within surface epithelium/crypt epithelium
 - Monocytoid B-cell hyperplasia
- Advanced stage
 - Loss of normal lymphoid cell population replaced by benign plasma cell infiltrate, increased vascularity, absence of multinucleated giant cells

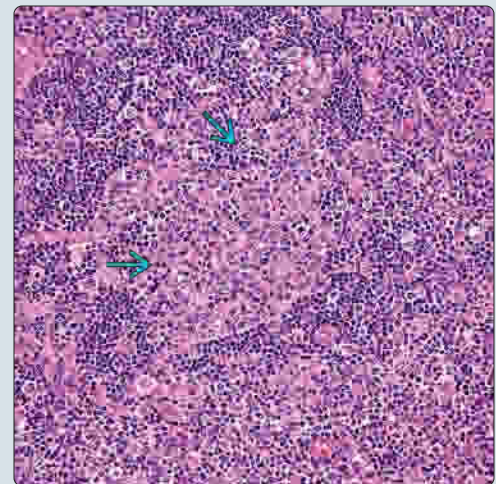
ANCILLARY TESTS

- Reactivity for HIV core antigen p24 (gag protein)

HIV Infection, Early to Chronic Phase

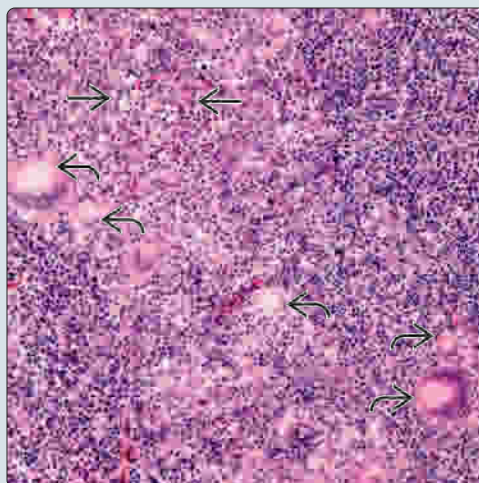


Follicle Lysis in Early to Chronic Phase

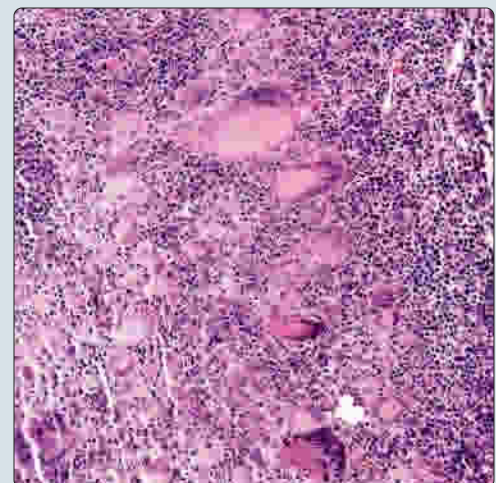


(Left) Early HIV infection of the tonsil includes florid follicular hyperplasia characterized by enlarged and irregularly shaped germinal centers, some approximating the surface epithelium. (Right) Higher magnification of a lymphoid follicle in the early to chronic phase of infection shows attenuated to partially absent mantle cell lymphocytes and follicle lysis, characteristic infiltration of the follicle by small lymphocytes, creating a "moth-eaten" appearance.

HIV Infection, Early to Chronic Phase



HIV Infection, Early to Chronic Phase



(Left) The presence of multinucleated giant cells (MGCs) is another characteristic feature of HIV infection. In this image the giant cells approximate compressed/obscured epithelium. (Right) Clustering of multinucleated giant cells (MGC) may or may not be present in a given case, but they tend to be a rather consistent feature in the early to chronic phase of HIV infection of tonsils and adenoids. While MGCs are present, well-formed granulomas are not seen.

TERMINOLOGY

Definitions

- Primary HIV infection of extranodal tissues of Waldeyer ring
 - Occurs in association with known systemic disease
 - May represent initial manifestation of HIV infection in patients not known to be HIV infected

ETIOLOGY/PATHOGENESIS

Infectious Agents

- HIV infection
 - Leads to destruction of cellular immunity, leading to immunosuppression, rendering host susceptible to opportunistic infections and tumors, a hallmark of AIDS
 - Belongs to human retrovirus of lentivirus genus
 - Preferentially infects CD4(+) (helper) T-cell lymphocytes and other cells of immune system that bear both CD4 receptor and 1 of 2 chemokine receptors (CCR-5 and CXCR-4) on their surface
 - Also includes dendritic cells and macrophages
 - Transmission occurs through
 - Blood
 - Sexual contact (bodily fluids)
 - Maternofetal routes

CLINICAL ISSUES

Epidemiology

- Incidence
 - More than 30 million persons are infected with HIV-1 worldwide
 - Majority of early cases in Western countries reported in men who have sex with men (homosexual and bisexual)
 - Remains major risk group (53%)
 - But highest increased incidence in intravenous drug users (36%) and women (18%) in USA
 - Most cases in Africa and Asia heterosexually transmitted
- Age
 - Occurs most frequently in 3rd-5th decades (median: 4th decade)
 - May occur in pediatric age groups
- Sex
 - Male > female

Site

- Nasopharyngeal tonsil (adenoids) and palatine tonsils

Presentation

- Clinical presentation varies, including
 - Nasal congestion
 - Airway obstruction
 - Sore throat (pharyngitis)
 - Otitis media unresponsive to antibiotic therapy
 - Otalgia, facial weakness, fever
 - Nasopharyngeal or tonsillar mass
 - Usually bilateral tonsillar or adenoidal enlargement but may be unilateral
 - Large ulcers may be present
 - Concurrent cervical adenopathy may be present
 - May raise concern for neoplastic (hematolymphoid or epithelial) proliferation

Laboratory Tests

- Serologic evaluation confirmatory for HIV infection

Treatment

- Options, risks, complications
 - Antiretroviral chemotherapy
 - Approach known as highly active antiretroviral therapy (HAART)
 - Antiretroviral therapy can reliably reduce viral loads to levels below 50 copies/ml when circulating virus is susceptible to available drugs
 - When viral loads are reduced to low levels, further immune decline is usually prevented and immune function is usually improved
 - Most patients with effective virologic suppression demonstrate improvement in CD4 count, but a few patients will not show benefit for unknown reasons
 - As HIV-infection of Waldeyer tonsillar ring may be initial manifestation of HIV infection, recognition of its pathologic features is essential to initiation of antiretroviral therapy
- Surgical approaches
 - Presence of mass may raise concern for neoplastic proliferation, prompting surgical removal of adenoids or tonsils

Prognosis

- Early management with antiretroviral chemotherapy may significantly prolong life and disease-free interval

MICROSCOPIC

Histologic Features

- Histomorphologic changes represent continuum, varying according to duration and progression of disease
- Acute &/or chronic stage
 - Florid follicular hyperplasia ± follicular fragmentation
 - Follicle lysis with areas of follicular involution
 - Monocytoid B-cell hyperplasia
 - Paracortical and interfollicular zone expansion with immunoblasts and plasma cells
 - Interfollicular clusters of high endothelial venules
 - Intrafollicular hemorrhage
 - Multinucleated giant cells (MGCs)
 - Characteristically cluster adjacent to or within adenoidal surface epithelium or tonsillar crypt epithelium
- Advanced stage
 - Features correlate with lymphoid obliteration seen in terminal stages of HIV infection or AIDS
 - Effacement of nodal architecture
 - Loss of normal lymphoid cell population replaced by benign plasma cell infiltrate
 - Presence of increased vascularity
 - MGCs characteristically seen in early and chronic stages of disease are not identified in more advanced stages

ANCILLARY TESTS

Histochemistry

- Special stains for microorganisms (other than HIV) negative

Immunohistochemistry

- Reactivity for HIV core antigen p24 (gag protein)
 - Indicator of active HIV infection consistently identified in early and chronic stages of disease
 - Anti-HIV p24 reactivity
 - Within follicular dendritic cell (FDC) network of germinal centers
 - Scattered interfollicular lymphocytes
 - Multinucleated giant cells
 - Intraepithelial cells of crypt epithelium
 - HIV p24(+) intraepithelial multinucleated giant cells are S100 protein (dendritic cell marker) positive
 - Morphologic appearance correlates with appearance of dendritic cells (DC)
- Reactivity with B-cell (CD20) and T-cell markers or subsets (CD45RO, CD3, OPD4)
 - Seen within germinal centers and interfollicular regions, as well as in scattered intraepithelial cells
- Advanced stages of disease
 - Relative absence of lymphoid cell markers (CD45RB, CD3, or OPD4)
 - Plasma cell infiltrate shows reactivity with κ and λ light chains indicative of benign proliferation
- Absent immunoreactivity for
 - Epstein-Barr virus-latent membrane protein (EBV-LMP)
 - In situ hybridization for Epstein-Barr encoded RNA (EBER)
 - Herpes simplex virus (HSV)
 - Cytomegalovirus (CMV)
- Surface and crypt epithelia reactive for epithelial markers (cytokeratins, others)

Genetic Testing

- In situ hybridization for HIV RNA seen in
 - FDC network
 - MGCs
 - Mature lymphocytes localized to
 - Germinal centers
 - Interfollicular zones
 - Within surface &/or crypt epithelia

Electron Microscopy

- Presence of abundant HIV particles associated with complex FDC network

DIFFERENTIAL DIAGNOSIS

Infectious Diseases (Other Than HIV)

- May be characterized by granulomatous inflammation
 - \pm caseating necrosis
 - Mycobacterial diseases
 - Fungal infections
 - Sarcoidosis
- May be characterized by intranuclear inclusions
 - CMV
 - HSV
- Histochemical &/or immunohistochemical stains may confirm presence of another infectious agent
 - Acid-fast bacilli for mycobacterial disease
 - Immunoreactivity for CMV or HSV

Infectious Mononucleosis (IM)

- IM lacks constellation of histologic features present in HIV infection
- Marked cytologic atypia of cells in IM absent in HIV
- Serologic markers associated with IM

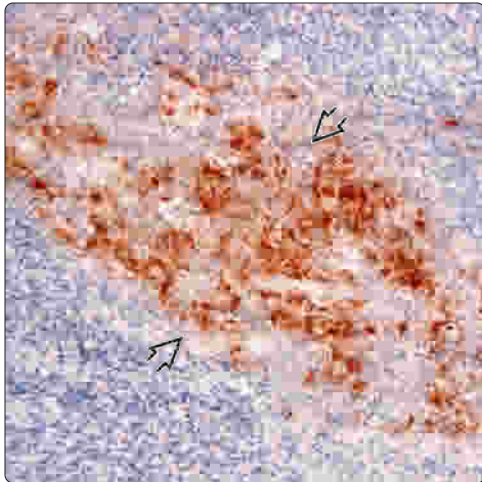
Non-Hodgkin Lymphoma

- Effacement of architecture with loss of germinal centers
- Most commonly large B-cell lymphomas
 - Sheet-like proliferation of dyscohesive cells with
 - Enlarged vesicular nuclei
 - Prominent eosinophilic nucleoli
 - Expression of B-cell antigens (i.e., CD20)
 - T-cell markers (-)
 - Absence of HIV p24 immunoreactivity
 - Monoclonality may be demonstrated by flow cytometry immunophenotyping as light chain restriction
 - Presence of gene rearrangements

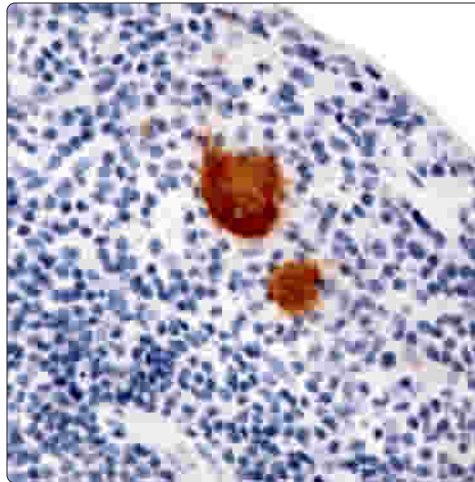
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p24 Immunohistochemical Staining

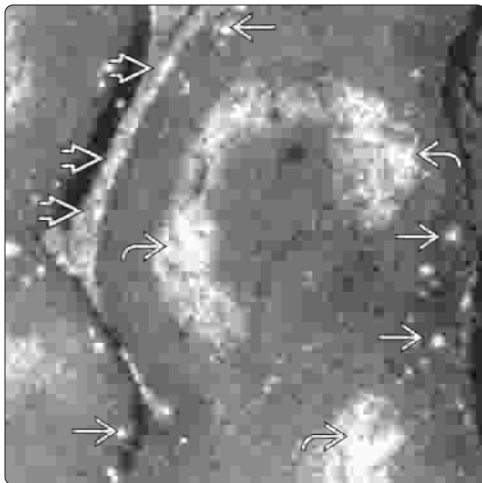


p24 Immunohistochemical Staining

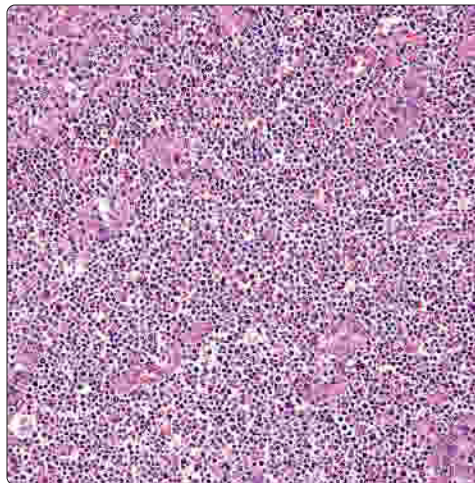


(Left) The constellation of light microscopic features suggest the possible presence of HIV infection, but confirmation is required. To this end, aside from serologic confirmation of HIV infection, the presence of HIV p24 immunoreactivity in follicular dendritic cells [X] is confirmatory of the diagnosis. (Right) In addition to the follicles, p24 immunoreactivity is also present in the multinucleated giant cells. These cells are also S100 protein positive.

In Situ Hybridization, Darkfield Microscopy

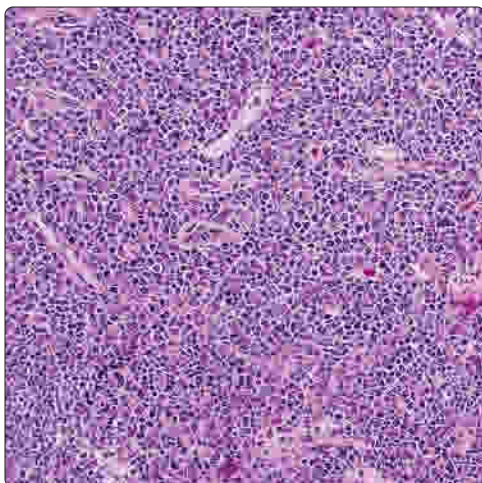


HIV Infection, Advanced Phase

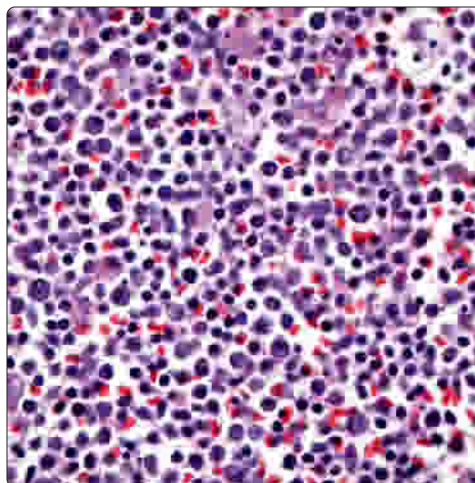


(Left) In situ hybridization for HIV-1 RNA using antisense riboprobe, darkfield microscopy shows signal in enlarged and irregularly shaped germinal centers [X], and in scattered multinucleated giant cells in interfollicular locations [Y] and within the epithelial layer [Z]. (Right) In more advanced stages, the findings include effacement of lymphoid architecture, loss of normal lymphoid cell population with replacement by a benign plasma cell infiltrate, and increased vascularity.

HIV Infection, Advanced Phase



HIV Infection, Advanced Phase



(Left) There is effacement of the normal architecture of the tonsils or adenoids with replacement by a benign plasma cell infiltrate, as well as the presence of increased vascularity. (Right) At higher magnification, the advanced phases of HIV infection shows an admixture of cell types, including benign plasma cells, mature lymphocytes, and histiocytes.

KEY FACTS

TERMINOLOGY

- Benign, highly cellular and richly vascularized mesenchymal neoplasm arising in nasopharynx in males

ETIOLOGY/PATHOGENESIS

- Activating β -catenin gene mutations

CLINICAL ISSUES

- Adolescents to young men (peak: 2nd decade)
- Recurrent, spontaneous epistaxis, nasal obstruction
- Nasopharynx is nearly always affected, with expansion (30% of cases)
- Selective angiography allows presurgical embolization with sclerosing agent or cryotherapy
- Surgery is treatment of choice, with endoscopic resection preferred
 - Biopsy is contraindicated due to potential exsanguination
- Recurrences in ~ 20% of patients

IMAGING

- Best seen on CT: Anterior bowing of posterior wall of maxillary sinus with posterior displacement of pterygoid plates (Holman-Miller sign)



MICROSCOPIC

- Range up to 22 cm in size
- Submucosal proliferation of vascular component within fibrous stroma
 - Many variably sized, disorganized vessels with patchy muscle content
 - Fibrous stroma consists of plump spindle, angular, or stellate-shaped cells
 - Variable amounts of fine and coarse collagen fibers

TOP DIFFERENTIAL DIAGNOSES

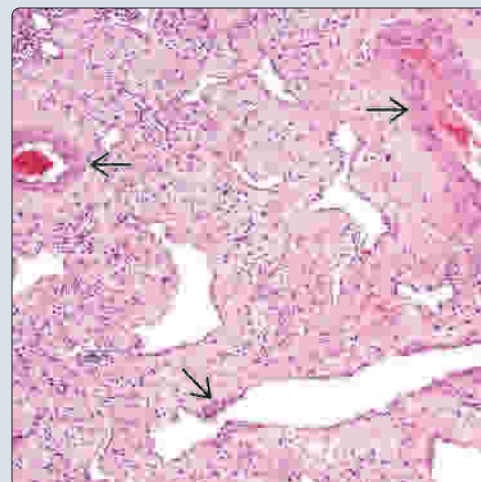
- Lobular capillary hemangioma
- Inflammatory polyp
- Antrochoanal polyp

Variety of Vessels in Fibrous Stroma




(Left) Hematoxylin & eosin shows an intact surface with a wide variety of vessels set within a fibrous stroma. Some of the vessels have smooth muscle and others do not. Patulous and compressed vessels are noted . (Right) There is a cellular fibrous connective tissue stroma surrounding the vessels in this juvenile angiofibroma. There is a difference in smooth muscle  identified around the different vessel types that comprise the tumor.

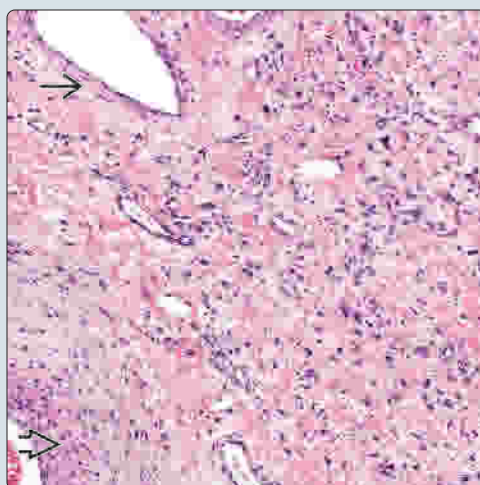


Variable Smooth Muscle Component



Cellular Fibrous Stroma With Focal Atypia

(Left) Hematoxylin & eosin shows smooth, muscle-walled vessels  adjacent to vessels without smooth muscle , along with numerous capillaries within a fibrous stroma. Isolated fibroblasts show nuclear pleomorphism. (Right) Hematoxylin & eosin shows numerous vessels of various calibers, some with smooth muscle  set in a heavily collagenized stroma. The stroma shows hypocellularity.



Complex Vascular Proliferation



TERMINOLOGY

Definitions

- Benign, highly cellular and richly vascularized mesenchymal neoplasm arising in nasopharynx exclusively in males

ETIOLOGY/PATHOGENESIS

Hormonal

- Testosterone-dependent, puberty-induced growth can be blocked with estrogen &/or progesterone therapy

Genetic

- Activating β -catenin gene mutations
- No well-developed association with familial adenomatous polyposis

CLINICAL ISSUES

Epidemiology

- Incidence
 - < 1% of all nasopharyngeal tumors
- Age
 - < 20 years old
 - Adolescents to young men (peak: 2nd decade)
- Sex
 - Males **exclusively**
 - If diagnosed in female, studies of sex chromosomes required to confirm gender

Site

- Nasopharynx affected
 - Pterygoid region usually affected
- May expand to involve surrounding structures (30% of cases)
 - Anterior: Nasal cavity and maxillary sinus via roof of nasopharynx
 - Lateral: Temporal and infratemporal fossae via pterygomaxillary fissure, resulting in cheek or intraoral buccal mass
 - Posterior: Middle cranial fossa
 - Superior: Pterygopalatine fossa and orbit via inferior and superior orbital fissures resulting in proptosis
 - Medial: Contralateral side

Presentation

- Symptoms present for 12-24 months due to nonspecific findings
- Recurrent, spontaneous epistaxis
- Nasal obstruction, discharge, sinusitis, rhinolalia
- Facial deformity (proptosis), exophthalmia, diplopia
- Otitis media, tinnitus, deafness
- Headaches

Treatment

- Options, risks, complications
 - Benign tumor can show aggressive local growth
 - Biopsy is contraindicated due to potential exsanguination
 - Complications include facial paresthesia (16%), ophthalmoplegia (12%), intranasal crusting (12%)
- Surgical approaches

- Surgery is treatment of choice, with endoscopic resection preferred
 - Endoscopic resection associated with less blood loss and fewer postoperative complications
- Definitive resection is frequently associated with significant morbidity
- Drugs
 - Preoperative estrogen hormone therapy
 - Not popular since giving estrogens to pubertal males is undesirable
 - Antiangiogenic therapy may be target in future
- Radiation
 - Used to manage large, intracranial, or recurrent tumors
- Angiography
 - Selective angiography allows embolization with sclerosing agent or cryotherapy

Prognosis

- Good
- May have fatal exsanguination if incorrectly managed
- Recurrences in ~ 10-20% of patients
 - Usually develop within 2 years of diagnosis, with intracranial extension

IMAGING

General Features

- Best seen on CT: Anterior bowing of posterior wall of maxillary sinus with posterior displacement of pterygoid plates (Holman-Miller sign)
- Angiography identifies feeding vessel(s) and tumor blush, allowing for presurgical embolization

MACROSCOPIC

General Features

- Polypoid, red, gray-tan mass with multinodular contour
- Size**
- Mean: 4 cm; range: Up to 22 cm

MICROSCOPIC

Histologic Features

- Submucosal proliferation of vascular component within fibrous stroma
- Many variably sized disorganized vessels
 - Varying thickness of vessel wall with patchy muscle content
 - Vessels are mostly thin-walled, slit-like (staghorn)
 - Range from capillary size to large, dilated, patulous vessels
- Focal, pad-like, smooth muscle thickenings within vessel walls
- Endothelial cells may be plump but are usually attenuated
- Fibrous stroma consists of plump spindle, angular, or stellate-shaped cells
- Variable amounts of fine and coarse collagen fibers
- Myxoid degeneration is common (especially in embolized specimens)
 - May see foreign material within vessels in embolized cases

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
Vimentin	Positive	Cytoplasmic	All elements of tumor
Actin-sm	Positive	Cytoplasmic	Smooth muscle of vessel walls highlighted
Desmin	Positive	Cytoplasmic	Only within larger vessel walls
Androgen receptor	Positive	Nuclear	Stromal cells and endothelial cell nuclei
β-catenin	Positive	Nuclear	Nuclear accumulation in stromal cells (not endothelial cells)
ER	Positive	Nuclear	Variably reactive, mostly in vascular nuclei
PR	Positive	Nuclear	Variably reactive, mostly in vascular nuclei
FVIIIIRAg	Positive	Cytoplasmic	Endothelial cells only
CD34	Positive	Cytoplasmic	Endothelial cells only
CD31	Positive	Cytoplasmic	Endothelial cells only
PDGF-B	Positive	Cytoplasmic	
IGF-2	Positive	Cytoplasmic	
S100	Positive	Nuclear & cytoplasmic	Highlights entrapped nerves but not tumor cells

Staging for Nasopharyngeal Angiofibroma

Stage	Radiographic, Clinical, or Pathologic Finding
I	Tumor limited to nasopharynx/nasal cavity with no bone destruction
II	Tumor invading nasal cavity, maxillary, ethmoid, and sphenoid sinus with no bone destruction
III	Tumor invading pterygopalatine fossa, infratemporal fossa, orbit, and parasellar region
IV	Tumor with massive invasion of cranial cavity, cavernous sinus, optic chiasm, or pituitary fossa (Sessions and Radkowi III A/B)

Composite staging based on Fisch, et al., Chandler, et al., Sessions, et al., Radkowski, et al., and Onerci, et al.

- As stroma increases, vascular compression results in virtually nonexistent lumina
- Elastic tissue is not identified within stroma
- Stromal cells may be angulated, multinucleated, and pleomorphic
- Mitotic figures are sparse
- Mast cells may be seen
- Hormone-treated cases show increased collagenization of stroma with fewer, but thicker-walled vessels
- Sarcomatous transformation is exceedingly uncommon event
 - Develops following massive doses of radiation

ANCILLARY TESTS

Histochemistry

- Reticulin shows positive black staining around stromal cells and blood vessels
- Elastic van Gieson highlights elastic tissue within vessel walls

Immunohistochemistry

- Vessels are highlighted within myofibroblastic stroma

DIFFERENTIAL DIAGNOSIS

Lobular Capillary Hemangioma

- Lesion is ulcerated; arises from different anatomic site; has granulation-type tissue and lots of inflammation; vessels are more organized

Inflammatory Polyp

- Especially if there are atypical stromal cells; usually more edematous; lacks rich vascular investment

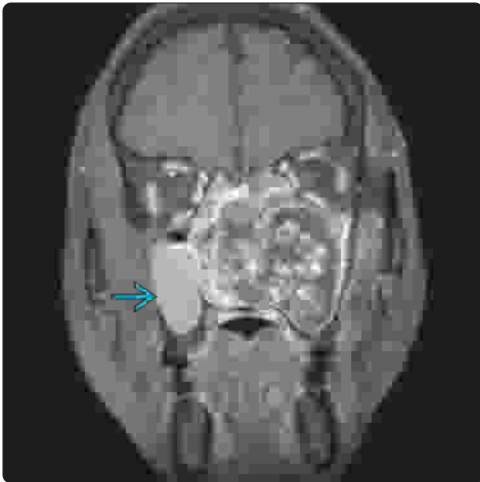
Antrochoanal Polyp

- Arises from different location; heavy stromal fibrosis but usually lacks characteristic vascular pattern of juvenile angiofibroma

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MR Shows Large Midline Mass

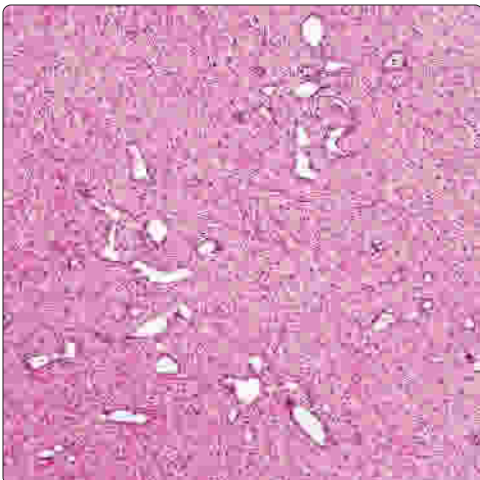


Gross Image of Angiofibroma

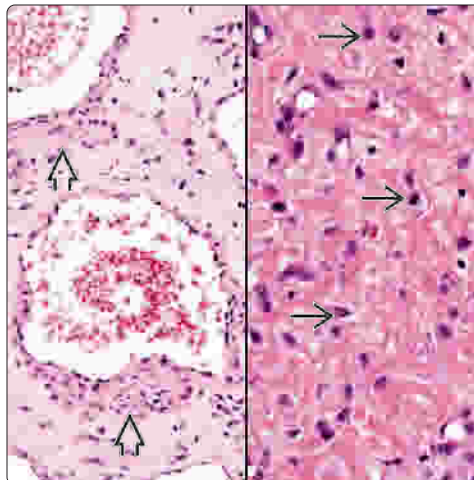


(Left) MR shows intracranial extension of a large, destructive, hyperintense mass in the nasopharynx. The bone has been remodeled and pushed aside. Note the fluid collection in the sinuses as a postobstructive phenomenon. (Right) It is not uncommon for a nasopharyngeal angiofibroma to expand into adjacent structures, creating a cast of the surrounding structures. In this image, the turbinate outlines are created due to tumor compression of these structures.

Cellular Fibrous Connective Tissue Stroma

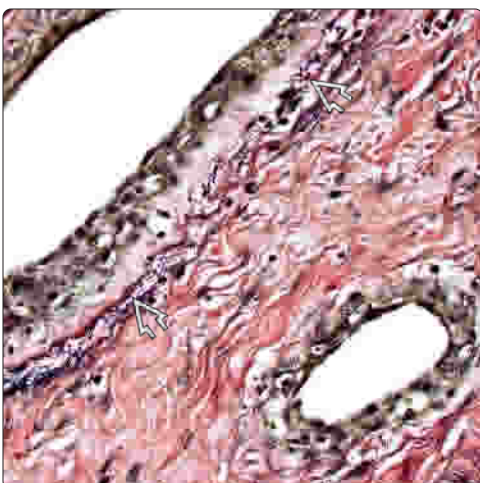


Mast Cells Are Easily Identified

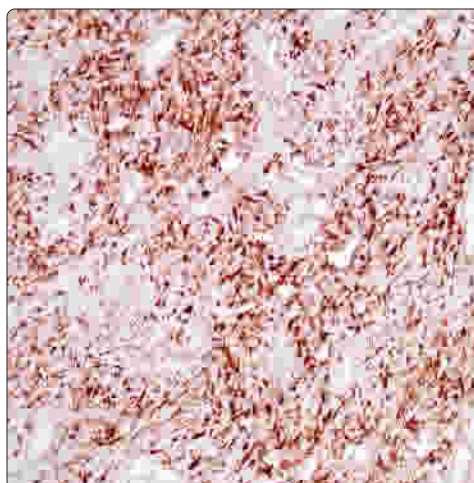


(Left) Hematoxylin & eosin shows increased collagen deposition, often seen in lesions of a long duration. Note how the vessels are compressed and narrowed to a nearly slit-like configuration. (Right) Hematoxylin and eosin shows a pad of smooth muscle within the vessel wall. The vessel contains erythrocytes. Note the increased number of mast cells in the stroma, which has wavy collagen deposition.

Altered Elastic Tissue in Vessel Walls



β -Catenin Nuclear Reaction



(Left) Elastic von Gieson shows elastic tissue (black deposition as short to wavy fragments) in the larger vessel but not in the smaller vessels. This results in profuse epistaxis, as the vessels are unable to contract and staunch bleeding. (Right) β -catenin shows nuclear accumulation specifically in the stromal cells, while the endothelial cell nuclei are negative. This is a helpful finding in this tumor.

KEY FACTS

TERMINOLOGY

- Developmental (congenital) anomaly predominantly composed of ectodermal and mesodermal tissue but lacking endodermal-derived tissues
- Also referred to as nasopharyngeal dermoid or teratoid lesion

ETIOLOGY/PATHOGENESIS

- Presence of skin suggests classification as choristoma
- Possibly of 1st branchial arch origin

CLINICAL ISSUES

- Majority of cases occurring in infantile period occurring in newborns or infants
- Predilection for female infants
- Primarily arises in nasopharynx
 - May arise in other areas of pharynx including oropharynx, as well as in association with eustachian tube and in middle ear

- Difficulties in breathing, swallowing, or sucking
- Cured following surgical resection




MICROSCOPIC

- Combination of various ectodermal and mesodermal tissues including
 - Skin (keratinizing squamous epithelium) and cutaneous adnexa
 - Cartilage, bone, muscle, fibrous tissue, mature adipose tissue, vascular tissue
- Polypoid lesions covered by
 - Skin with identification of hair follicles and sebaceous glands within dermis/submucosa and identification of elastic cartilage

TOP DIFFERENTIAL DIAGNOSES

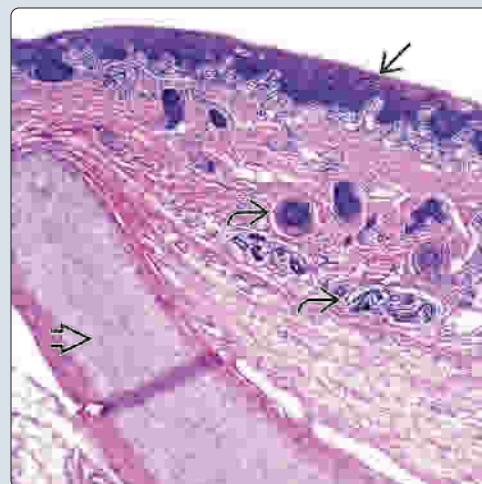
- Teratoma
 - Represents true neoplasm composed of tissues from all 3 germ layers

Hairy Polyp




(Left) Hairy polyp is also known as a nasopharyngeal dermoid. This lesion occurred in a neonate with airway obstruction and appears as a polypoid solid mass with identifiable hairs on the surface. **(Right)** The histology of hairy polyp includes a combination of ectodermal and mesodermal tissues, such as keratinizing squamous epithelium , adnexal structures , and cartilage . There is an absence of endodermal structures.

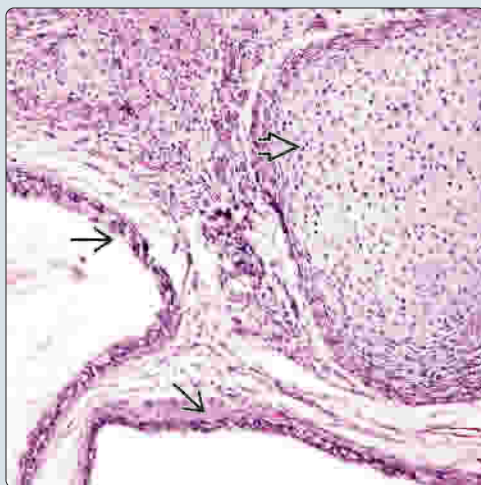


Hairy Polyp

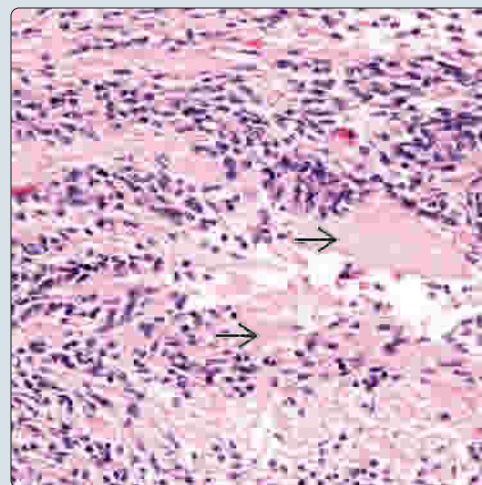


Teratoma

(Left) Histologically, teratomas are comprised of elements from all germ cell layers, including ectodermal, mesodermal, and endodermal structures. In this image, epithelial-lined glands  and immature cartilage  are present. **(Right)** In addition to endodermal (e.g., glands) and mesodermal (e.g., cartilage) structures, teratomas may include a neuroglial tissue as illustrated here by the presence of a cellular proliferation with neurofibrillary matrix .



Teratoma



TERMINOLOGY

Synonyms

- Nasopharyngeal dermoid or teratoid lesion

Definitions

- Developmental (congenital) anomaly predominantly composed of ectodermal and mesodermal tissue but lacking endodermal-derived tissues

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Proposed classification includes
 - 1st branchial arch origin
 - Presence of skin, including hair follicles and sebaceous glands and identification of elastic cartilage
 - Findings identical to those of congenital accessory auricles akin to accessory tragus, which is of 1st branchial arch origin
 - Choristoma
 - Suggested by presence of skin, tissue type not normally found in nasopharynx
 - Teratoma
 - On basis of histologic features, some authorities feel these lesions are best classified as subset of benign teratoma
 - Absence of endodermal-derived structures and presence of limited heterogeneity of tissue types argue against inclusion as benign teratoma

CLINICAL ISSUES

Epidemiology

- Age
 - Majority of cases occurring in infantile period occurring in newborns or infants
- Sex
 - Predilection for female infants

Site

- Primarily arises in nasopharynx
 - May arise in other areas of pharynx, including oropharynx, as well as in association with eustachian tube and in middle ear

Presentation

- Difficulties in breathing, swallowing, or sucking

Treatment

- Surgical approaches
 - Simple surgical excision is treatment of choice

Prognosis

- Cured following surgical resection

MACROSCOPIC

General Features

- Polypoid, predominantly solid, but partially cystic, lesions
- May be pedunculated or sessile

MICROSCOPIC

Histologic Features

- Combination of various ectodermal and mesodermal tissues including
 - Ectodermal structures
 - Skin (keratinizing squamous epithelium)
 - Cutaneous adnexa
 - Mesodermal structures
 - Cartilage, bone
 - Muscle (striated or smooth)
 - Fibrous tissue
 - Mature adipose tissue
 - Vascular tissue
- Polypoid lesions covered by
 - Skin with identification of hair follicles and sebaceous glands within dermis/submucosa and identification of elastic cartilage
 - These histologic findings suggest branchial cleft origin representing congenital accessory auricles akin to accessory tragus

DIFFERENTIAL DIAGNOSIS

Teratoma

- Represents true neoplasm composed of tissues from all 3 germ layers
- Presence of endodermal-derived tissue and presence of wide variety of tissue types usually seen in teratoma will allow for distinguishing these lesions

Epidermal Inclusion Cyst

- Lined by stratified squamous epithelium with keratin-filled cyst; lacks adnexal structures in cyst wall

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KEY FACTS

TERMINOLOGY

- Type of squamous cell carcinoma originating from nasopharyngeal mucosa with evidence of squamous differentiation by light microscopy &/or immunohistochemistry

ETIOLOGY/PATHOGENESIS

- Strong association with EBV
- HPV has been reported in nasopharyngeal carcinomas (NPCs)

CLINICAL ISSUES

- Uncommon neoplasm in USA, accounting for ~ 0.25% of all cancers
- In China, NPC accounts for 18% of all cancers
- May present as asymptomatic cervical neck mass
 - Primary carcinoma often occult
- Lateral wall (fossa of Rosenmüller) > superior posterior wall


- Supervoltage radiotherapy (50-80 Gy) ± adjuvant chemotherapy considered treatment of choice
- Overall 5-year survival (~ 75%)

MICROSCOPIC

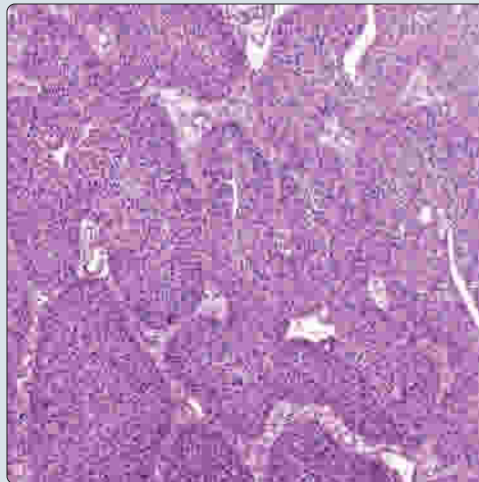
- **NPC, differentiated type**
 - Interconnecting cords or trabeculae composed of stratified cells with pleomorphic, hyperchromatic nuclei showing little to absent keratinization
- **NPC, undifferentiated type**
 - Cohesive (syncytial) growth to diffuse cellular infiltrate composed of dyscohesive cells that are made of enlarged round nuclei with vesicular chromatin and prominent eosinophilic nucleoli

ANCILLARY TESTS

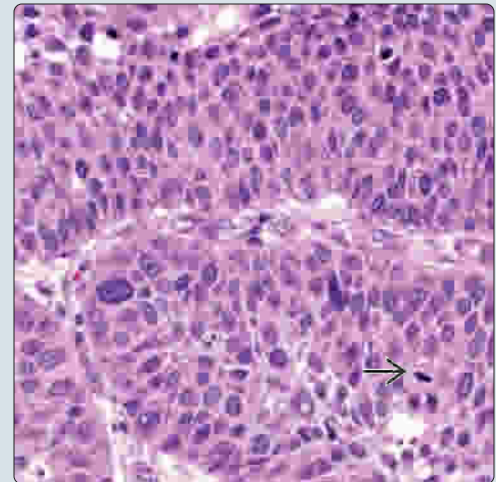
- Strong immunoreactivity for cytokeratins and p63 (nuclear)
- In situ hybridization for Epstein-Barr encoded RNA (EBER)
 - Considered gold standard and includes strong and diffuse nuclear staining


(Left) Nasopharyngeal carcinoma (NPC), nonkeratinizing differentiated type, is characterized by broad interconnecting cords and trabeculae of infiltrative carcinoma. This pattern of growth is indicative of an infiltrative neoplasm. **(Right)** At higher magnification, the neoplastic cells of NPC, nonkeratinizing differentiated type, are stratified with nuclear pleomorphism, increased nuclear to cytoplasmic ratio, and increased mitotic activity .

NPC, Nonkeratinizing Differentiated Type

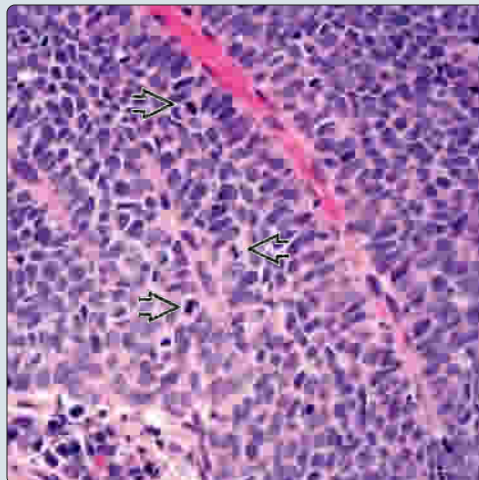


NPC, Nonkeratinizing Differentiated Type

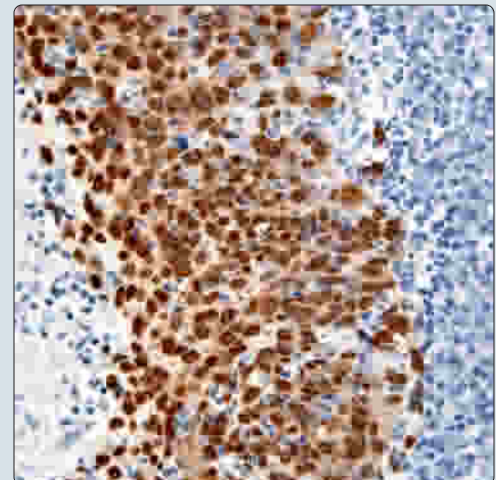


(Left) NPC, nonkeratinizing differentiated type, shows limited cytologic atypia, but mitoses, including atypical forms are readily identified . **(Right)** In situ hybridization for Epstein-Barr (EBV)-encoded RNA (EBER) shows diffuse and strong reactivity of the tumor cell nuclei. The presence of EBER staining confirms the diagnosis. EBER should not be confused with immunohistochemical staining for EBV latent membrane protein (EBV-LMP). EBV-LMP is less sensitive and specific than EBER.

NPC, Nonkeratinizing Differentiated Type



NPC, Nonkeratinizing Differentiated Type



TERMINOLOGY

Abbreviations

- Nasopharyngeal carcinoma (NPC)

Synonyms

- Lymphoepithelioma, Rigaud and Schmincke types; transitional carcinoma
 - Lymphoepithelioma is misnomer
 - Tumor entirely of epithelial origin with secondary associated benign lymphoid component
 - Designations Rigaud and Schmincke refer to syncytial vs. individual cell growth patterns, respectively, with no biologic import

Definitions

- Type of squamous cell carcinoma originating from nasopharyngeal mucosa with evidence of squamous differentiation by light microscopy &/or immunohistochemistry
- WHO classification of NPC
 - I: Keratinizing squamous cell carcinoma (represent ~25% of all cases)
 - II: Nonkeratinizing
 - Differentiated (represent ~ 15% of all cases)
 - Undifferentiated (represent ~ 60% of all cases)
 - III: Basaloid squamous cell carcinoma

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Nonkeratinizing types have very strong association with Epstein-Barr virus (EBV)
 - Strong association indicates oncogenic role of EBV in development of NPC
 - EBV early initiating event in development of NPC
 - EBV found in preinvasive (precursor) nasopharyngeal lesions
 - Clonal episomal EBV-DNA identified, suggesting viral entry into nucleus before clonal expansion
 - Human papillomavirus (HPV) has been reported in NPCs of keratinizing and nonkeratinizing types
 - HPV may have pathogenetic role for some NPCs
 - HPV-associated NPC may be morphologically similar to EBV-associated carcinomas but are negative for EBER and positive for p16
 - Tend to occur in nonendemic populations, including Caucasians with history of smoking

Environmental Exposure

- Purported risk factors include
 - High dietary levels of volatile nitrosamines in salt-preserved or fermented foods in high-incidence regions implicated as carcinogen
 - Conversely, high consumption of fresh fruits and vegetables lowers risk of NPC in endemic regions
 - Cigarette smoking
 - Occupational exposure to chemical fumes, smoke, formaldehyde
 - Prior radiation exposure

Genetic and Geographic Factors

- Familial clustering yields 10x familial RR (highest genetic association for all types of cancer)
- Incidence among Chinese people decreases after emigration to low-incidence areas but still remains higher than in non-Chinese populations

CLINICAL ISSUES

Epidemiology

- Incidence
 - Overall, NPC is uncommon neoplasm in USA, accounting for ~ 0.25% of all cancers
 - In China, NPC accounts for 18% of all cancers, and 1 in 40 men develop NPC before age 72
- Age
 - Most common in 4th-6th decades
 - Nonkeratinizing types may occur in pediatric patients
 - > 20% occur in pediatric age groups
 - Pediatric NPC most common in northern and central Africa, accounting for 10-20% of all cases
 - ~ 2% of NPC in China occurs in children
- Sex
 - Male > female (3:1)
- Ethnicity
 - Endemic populations include southern China (including Hong Kong), Southeast Asia, Malaysia, Northern Africa, Middle East, Arctic

Site

- Lateral wall (fossa of Rosenmüller) > superior posterior wall

Presentation

- Presence of asymptomatic cervical neck mass typically localized to posterior cervical triangle, or superior jugular nodal chain is commonly present
 - Can be present in up to 50% of patients as initial presentation for NPC
 - Primary carcinoma is often occult with no correlation to size of primary NPC, which may be extremely small (few mms) and size of nodal metastasis, which may be large (centimeters)
 - Bilateral cervical neck metastasis may be seen in up to 25% of cases
- Additional signs and symptoms may include
 - Nasal obstruction, nasal discharge, epistaxis, pain, serous otitis media, otalgia, hearing loss, headache
- Signs and symptoms in early stages often subtle and nonspecific, resulting in delay of diagnosis
 - Presentation often at more advanced clinical stage
- Up to 25% of patients may experience cranial nerve involvement
 - Considered adverse prognostic finding
 - Cranial nerves involved may include
 - III, IV, ophthalmic branch of V, 3rd division of V (through parapharyngeal space in proximity to lateral nasopharyngeal wall), VI, IX-XII

Laboratory Tests

- Positive serology against EBV in > 90% of patients reported
 - Elevated titers of IgA antibodies (vs. viral capsid antigen [VCA]) and IgG antibodies (vs. early antigen [EA])

- Detection rates range up to 93%
- Elevated titers used as marker to screen populations in high-risk areas and as potential indicator of disease relapse
- Quantitative PCR testing for elevated circulating EBV-DNA in plasma and serum reported sensitivity rates of up to 96%
- Molecular biologic analysis of NPC by either in situ hybridization, PCR detects EBV-DNA, or RNA in 75-100% of NPCs
 - Not true of keratinizing subtype, in which detection of EBV genomes is variable and, if present, is generally limited to scattered dysplastic intraepithelial cells
- Expression of EBV nuclear antigen-1 (EBNA-1), latent membrane protein-1 (LMP-1), EBV-encoded RNA (EBER)
- EBV-encoded miRNAs in circulation aid in early detection (biomarkers) and potential therapeutic agents in future
- Elevated levels of circulating cell-free EBV-DNA detected in plasma and serum samples from NPC patients
 - Good sensitivity and specificity; might be helpful for screening of NPC
- Presence of lymph node metastasis decreases survival by ~ 10-20%
- Large percentage of NPCs, particularly undifferentiated type, metastasize to sites below clavicle, including lungs, bone (ribs and spine), liver
 - Associated with worse prognosis
- Children and adolescents tend to present at more advanced clinical stage, but still retain relatively good rate of long-term survival (yet are prone to serious long-term treatment-related morbidities)
- Risk of developing synchronous or metachronous 2nd primary malignancy is ~ 4%

IMAGING

Radiographic Findings

- Important diagnostic aid in assessing extent of disease and presence of metastatic disease
- Positron emission tomography and computed tomography (PET/CT) is used in detection of locoregional and distant spread of tumor

MR Findings

- Preferred study for detection of invasion into soft tissues, intracranial extension, and invasion into bone

MICROSCOPIC

Histologic Features

Treatment

- Due to anatomic constraints imposed by nasopharynx and tendency of NPCs to present with advanced stage, supravoltage radiotherapy (50-80 Gy) ± adjuvant chemotherapy is considered treatment of choice for all histologic subtypes
- Technical advances in treatment planning systems incorporating CT has led to development of conformational therapies, including 3-dimensional conformal therapy and intensity-modulated radiation therapy (IMRT)
 - Provides accurate delineation of tumor volumes and adjacent critical structures, allowing for achieving maximal therapeutic benefit
 - Fusion with MR or PET/CT crucial to accurately follow tumor spread 3 dimensionally

Prognosis

- Overall 5-year survival ~ 75%
- Clinical stage at presentation represents most important prognostic factor
 - 5-year disease-specific survival (DSS) for
 - Stage I: 98%
 - Stage IIA-B: 95%
 - Stage III: 86%
 - Stage IVA-B: 73%
- Long-term outcomes in patients treated with induction chemotherapy and radiotherapy (CRT) vs. radiotherapy alone (RT) show
 - Modest but significant decrease in relapse and improvement in DSS in advanced-stage NPC
 - Includes addition of cisplatin-based induction chemotherapy (cisplatin, bleomycin, fluorouracil [5-FU] or cisplatin, and epirubicin) to RT
 - No substantive improvement in overall survival reported
- Factors affecting prognosis may include
 - Better prognosis associated with lower clinical stage, younger patient age, female gender
 - Worse prognosis with higher stage tumors, older patients, male gender
 - Frequently metastasizes to regional lymph nodes

● NPC, differentiated type

- Growth includes presence of interconnecting cords or trabeculae
 - Cystic change with associated (central) necrosis commonly present
 - Often metastasizes to lymph nodes as cystic metastasis
- Stratified cells with pleomorphic, hyperchromatic nuclei showing little to absent keratinization
 - Well-defined cell borders and vague intercellular bridges may be present
 - Keratinized cells may be identified
 - Increased mitotic activity, including atypical mitoses
- Sharp delineation from surrounding stroma
- Typically, absence of desmoplastic stromal response to invasive growth

● NPC, undifferentiated type

- Variable growth, including cohesive (syncytial) or cell nests (Rigaud pattern) to diffuse cellular infiltrate composed of dyscohesive cells (Schminke pattern)
- Neoplastic cells characterized by
 - Enlarged round nuclei with vesicular chromatin, prominent eosinophilic nucleoli, scant eosinophilic to amphophilic cytoplasm, indistinct borders
 - Keratinization is typically absent, but in any case may be focally present
- Mitoses can be seen, but typically are not prominently present
- Prominent nonneoplastic lymphoid component composed of
 - Mature lymphocytes and plasma cells
 - May overrun and obscure invasive carcinoma
- Infiltrative growth generally does not produce host desmoplastic response

- Absence of desmoplasia in conjunction with prominent benign lymphocytic infiltrate obscuring lesional cells may make diagnosis problematic
- Absence of desmoplastic response may also be present in association with nodal metastasis
- Other uncommon cell types &/or growth patterns may include spindle-shaped neoplastic cells and reticulated growth pattern
- Uncommon to identify precursor lesion (i.e., intraepithelial dysplasia &/or carcinoma in situ)
 - Intraepithelial dysplasia can be seen in surface or crypt epithelium
 - Most cases of invasive carcinoma occur without identifying intraepithelial dysplasia/carcinoma in situ
 - NPC originates from nasopharyngeal surface &/or crypt epithelium, even in absence of identifying intraepithelial dysplasia &/or carcinoma in situ
- Since distinction between differentiated type from undifferentiated type is of no clinical or prognostic significance; subclassification into differentiated and undifferentiated subtypes is optional
 - Should be noted that histologically 26% of NPCs may have features of more than 1 tumor type, so classification is according to dominant component
 - Should also be noted that histologic distinction among 3 types of NPC may not always be clear with overlapping histology in any given tumor

ANCILLARY TESTS

Immunohistochemistry

- Strong immunoreactivity for cytokeratins including AE1/AE3, CAM5.2, CK5/6, OSCAR, and EMA
- p63 (nuclear) strongly and diffusely reactive
- **Positive** for EBV
 - Latent membrane protein 1 (LMP1) reactivity (considered to lack sensitivity)
 - In situ hybridization for Epstein-Barr encoded RNA (EBER)
 - Considered gold standard and includes strong and diffuse nuclear staining
 - Invariably present in nonkeratinizing subtypes (i.e., differentiated, undifferentiated), but not true of keratinizing subtype
- p16 immunoreactivity typically **negative**, but may be **positive** in NPC with morphology similar to EBV-associated carcinomas (yet will be **negative** for EBER)
- No immunoreactivity for hematolymphoid markers (**positive** in nonneoplastic lymphoplasmacytic infiltrate, including CD45, CD3, and CD20), melanocytic markers, myogenic markers

Genetic Testing

- Development of NPC likely involves cumulative genetic and epigenetic changes in background of predisposed genetic and environmental factors

DIFFERENTIAL DIAGNOSIS

Oropharyngeal Nonkeratinizing Carcinoma

- Share histomorphologic features with NPC, nonkeratinizing types
 - Such tumors are p16(+) and EBER(-)

- Nodal metastatic p16(+), EBER(-) carcinomas may originate from occult primary oropharyngeal carcinomas
- Work-up for nodal metastatic carcinomas with features of NPC, differentiated and undifferentiated, should include staining for EBER and p16

Diffuse Large B-Cell Lymphoma

- **Positive** for hematolymphoid markers, including CD45 (leucocyte common antigen) and B-cell markers
- **Negative:** Cytokeratins and EBV

Mucosal Malignant Melanoma

- **Positive:** S100 protein, melanoma-specific markers (HMB-45, Melan-A, tyrosinase, MITF, SOX10)
- **Negative:** Cytokeratins and EBV

Rhabdomyosarcoma

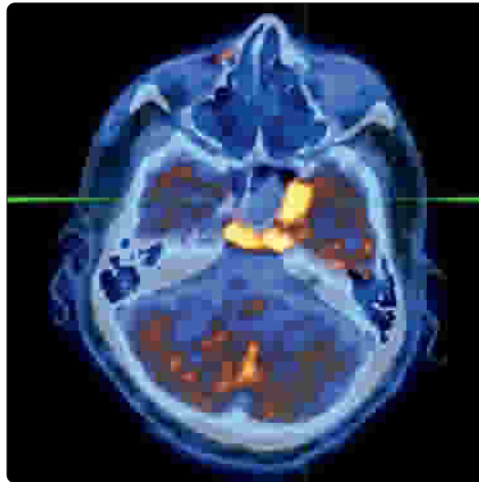
- **Positive:** Myogenic markers (desmin, myogenin)
- **Negative:** Cytokeratins and EBV

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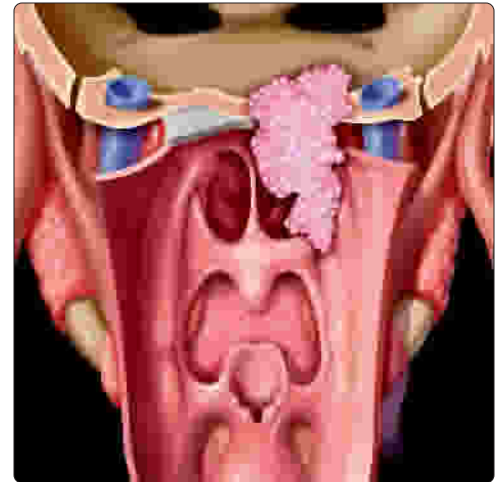
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Nasopharyngeal Carcinoma

(Left) PET image with a superimposed computed tomography scan demonstrates very high signal intensity in the nasopharyngeal region in this case of NPC. (Right) This graphic demonstrates a large mass in the nasopharynx that has expanded into the base of the skull. In general, most NPCs are small and may be clinically difficult to detect, but in some cases the carcinoma may be large and extensively infiltrative into adjacent vital structures.



NPC, Tumor Extent

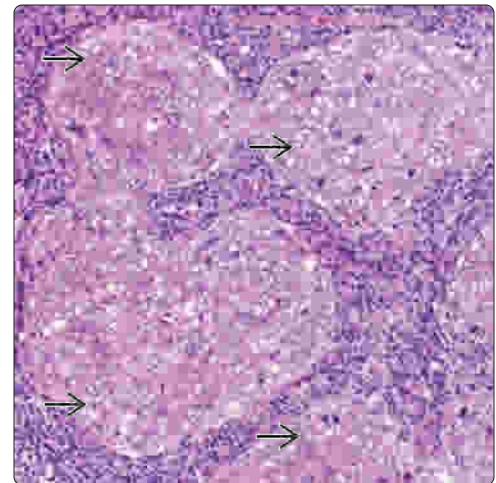


NPC, Skull Base Extension

(Left) Correlating to the depiction in the adjacent graphic illustration, this sagittal image shows a NPC extending from the nasopharynx into the skull base. (Right) Nonkeratinizing undifferentiated NPC is characterized by readily identifiable tumor nests demarcated from surrounding stroma, the latter lacking a desmoplastic reaction.

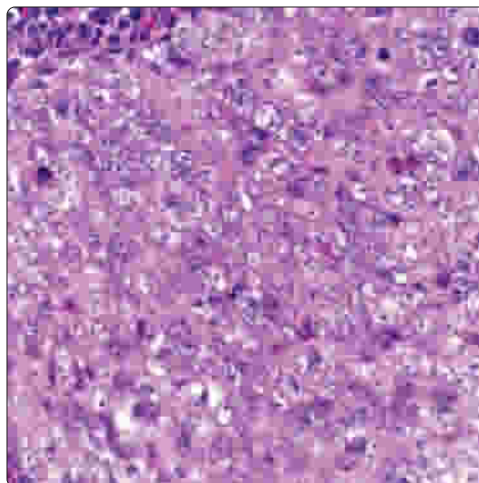


NPC, Nonkeratinizing Undifferentiated Type

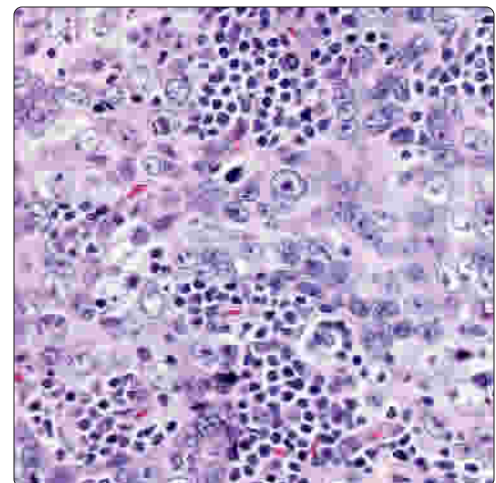


NPC, Nonkeratinizing Undifferentiated Type

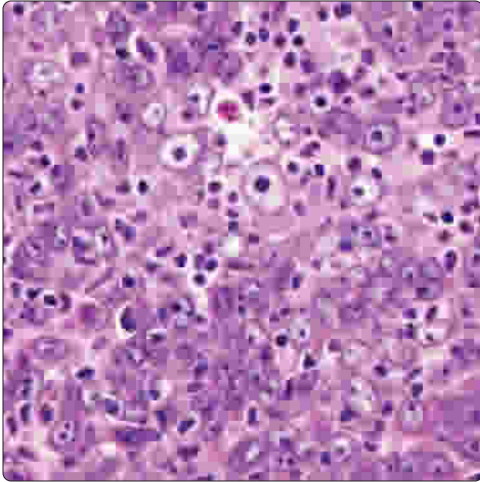
(Left) A cohesive (syncytial) pattern of growth composed of cells with enlarged oval to round nuclei with vesicular chromatin, prominent eosinophilic nucleoli, scant cytoplasm, and indistinct cell margins is shown. (Right) Clusters of malignant cells comprised of enlarged vesicular nuclei with prominent nucleoli with associated benign lymphocytic cell infiltrate are shown. In spite of the invasive growth, there is an absence of desmoplasia.



NPC, Nonkeratinizing Undifferentiated Type



NPC, Nonkeratinizing Undifferentiated Type

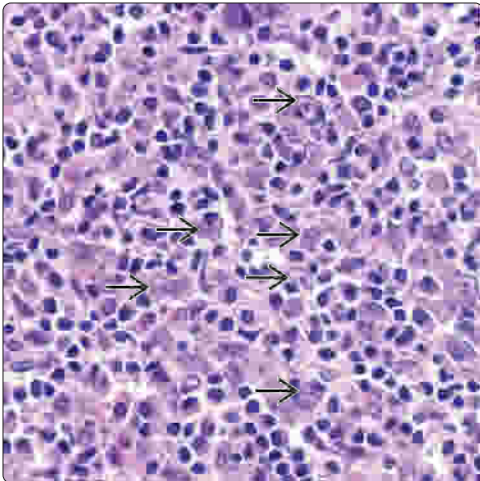


NPC, Nonkeratinizing Undifferentiated Type

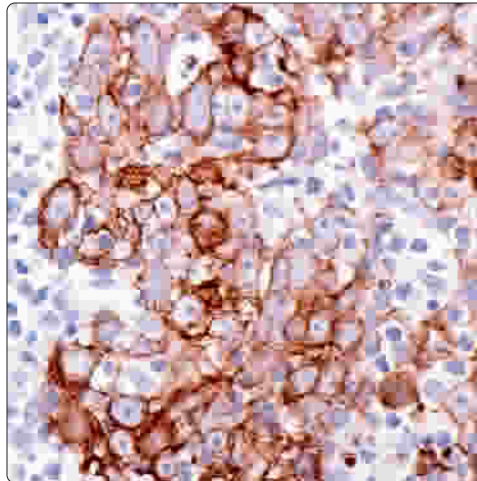


(Left) Diffuse pattern of growth composed of dyscohesive cells with enlarged vesicular chromatin & prominent nucleoli is shown. These features raise concern for a possible diagnosis of diffuse large B-cell lymphoma. Cytokeratin reactivity would confirm the diagnosis of NPC. **(Right)** At low magnification, there is no suggestion that an invasive carcinoma is present due to the absence of a host desmoplastic response to invasive NPC. Instead, the impression may be that of a mixed reactive inflammatory cell proliferation.

NPC, Nonkeratinizing Undifferentiated Type

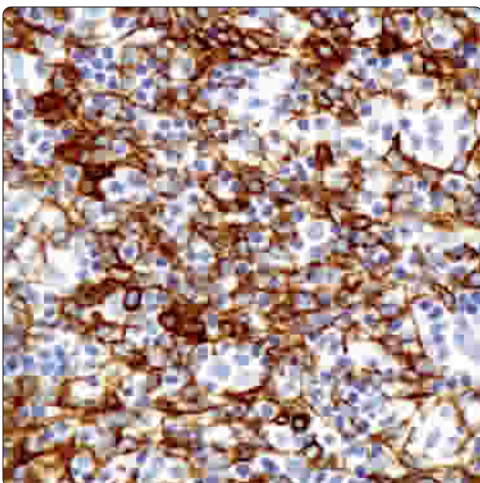


NPC, Cytokeratin Reactivity

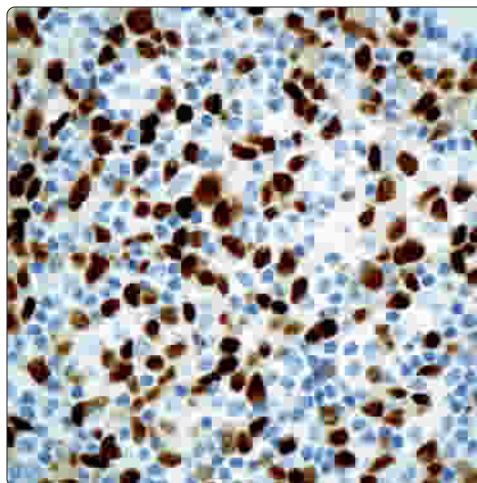


(Left) At higher magnification, the neoplastic cells are seen but may be easily overlooked and viewed as part of a reactive inflammatory cell infiltrate, given the absence of associated desmoplasia. Immunohistochemical staining is needed to confirm the diagnosis. **(Right)** The cohesive (syncytial) growth suggests an epithelial neoplasm but cytokeratin reactivity is required to confirm the cells as being epithelial and, therefore, diagnostic of NPC.

NPC, Cytokeratin Reactivity

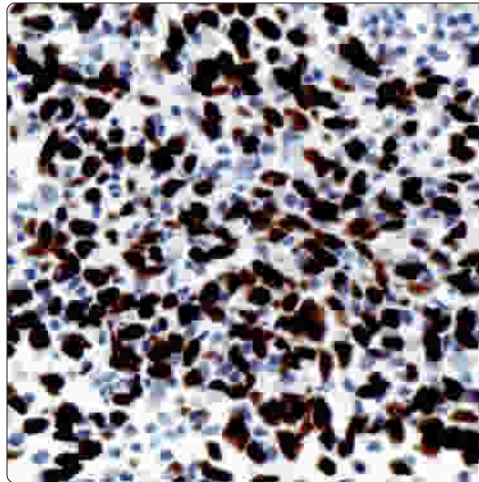


NPC, p63 Reactivity

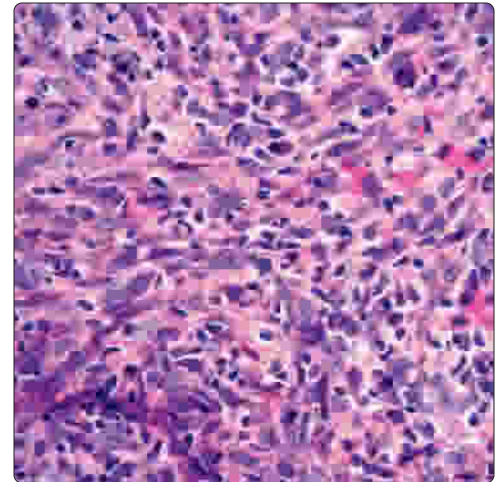


(Left) Dyscohesive growth, the presence of associated inflammatory cells, and the absence of desmoplasia obscure the malignant cells that show a meshwork pattern of cytokeratin reactivity, allowing for their identification and confirmation of the diagnosis. **(Right)** In addition to cytokeratins, the malignant cells irrespective of growth pattern are diffusely and strongly p63 reactive. The associated reactive lymphoid cell population is nonreactive with p63.

NPC, EBER Positive

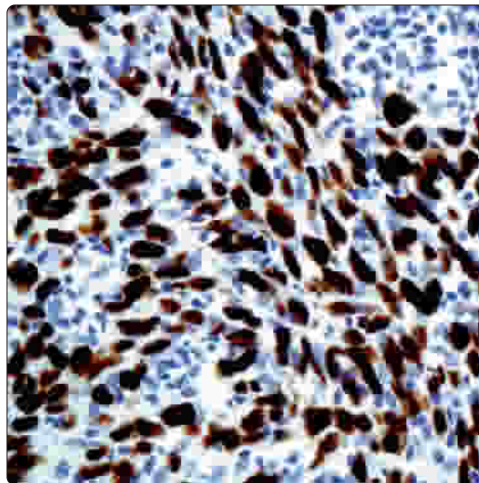


NPC, Spindle Cell Features

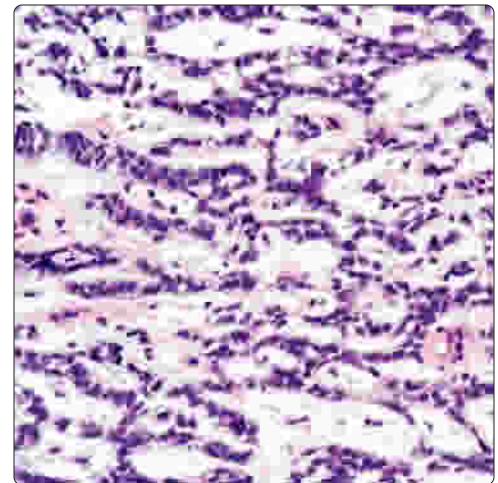


(Left) In situ hybridization for EBER shows diffuse and strong nuclear staining of the neoplastic cells, confirming the diagnosis of NPC. The associated reactive lymphoid cell population is EBER negative. **(Right)** Variant cytomorphic features in NPC may include the presence of spindle-shaped malignant cells. Similar to more usual cells types, there is an associated lymphoid cell proliferation and the absence of stromal desmoplasia in spite of infiltrative growth.

NPC, p63 Reactivity in Spindle Cells

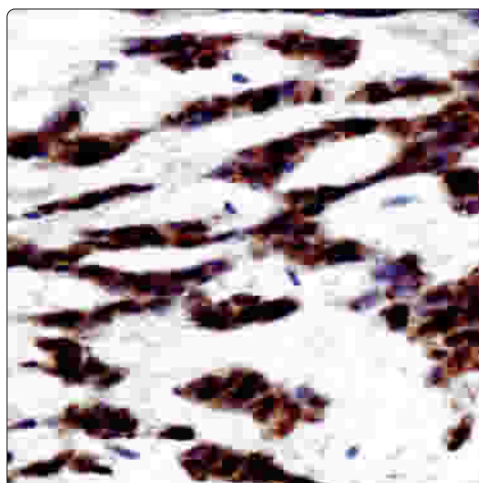


NPC, Reticulated Pattern

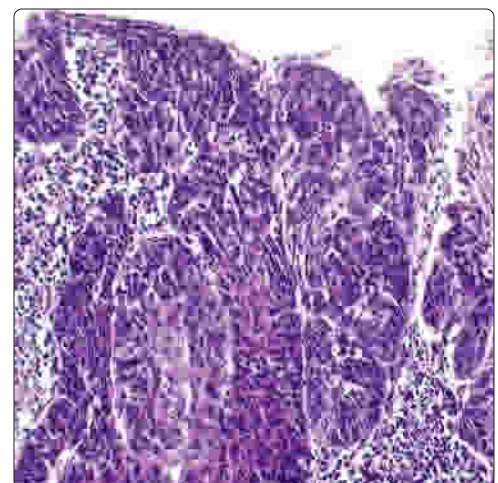


(Left) In addition to the presence of cytokeratin and p63 immunoreactivity (not shown), the spindle-shaped malignant cells show strong and diffuse nuclear EBER staining confirming the diagnosis of NPC. **(Right)** Variant growth in NPC may include a reticulated pattern, which is considered an unusual feature in association with NPC. Such a pattern may engender alternative diagnostic considerations, such as a minor salivary gland neoplasm.

NPC, EBER Positive Reticulated Pattern



NPC, Carcinoma In Situ

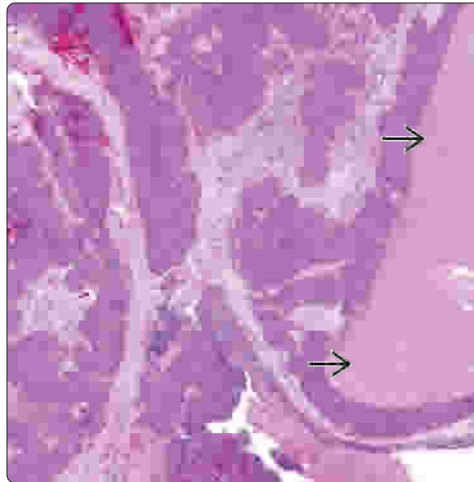


(Left) The presence of strong and diffuse nuclear EBER, in addition to cytokeratin and p63 immunoreactivity (not shown), would confirm the diagnosis of NPC. **(Right)** Carcinoma in situ is an uncommon finding in NPC, but on occasion may be identified. In most cases, invasive carcinoma occurs without identifying intraepithelial dysplasia or carcinoma in situ.

Metastatic NPC, Imaging Findings



Cystic NPC, Nonkeratinizing Differentiated Type

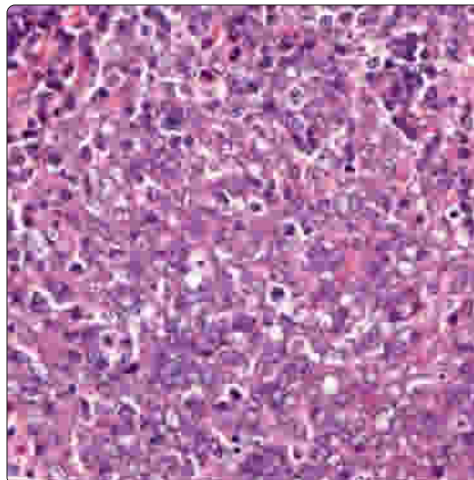


(Left) Coronal T1 C+ MR in a patient with NPC reveals bulky bilateral cervical adenopathy [red arrow]. Notice that a smaller, right lateral retropharyngeal node can also be seen near the skull base [blue arrow]. (Right) NPC, nonkeratinizing differentiated type, shows cystic degeneration characterized by a large cyst filled with necrotic material [black arrow]. This cystic appearance with associated necrosis is the pattern that can be seen when this carcinoma metastasizes to cervical lymph nodes (i.e., cystic metastatic nonkeratinizing carcinoma).

Metastatic NPC, Nonkeratinizing Undifferentiated Type

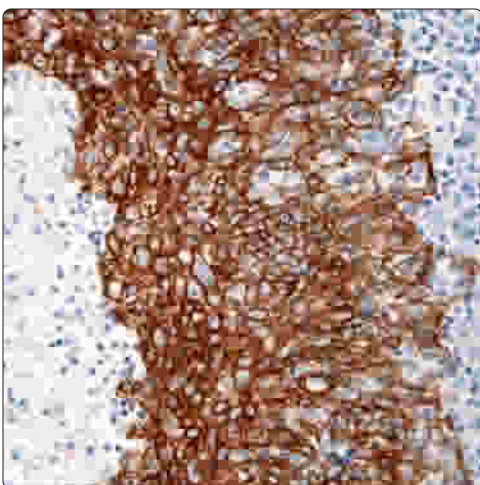


Metastatic NPC, Nonkeratinizing Undifferentiated Type

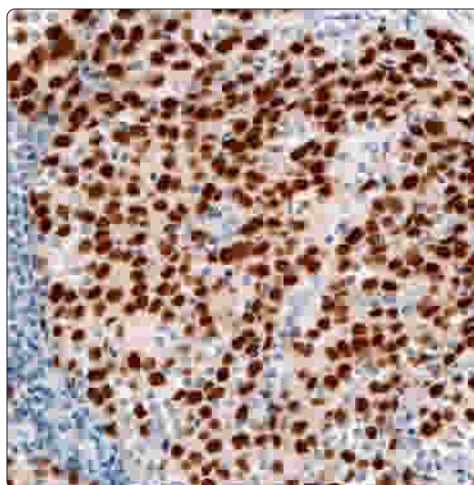


(Left) Nodal metastasis from a NPC, nonkeratinizing undifferentiated type, shows cystic degeneration and an absent desmoplastic reaction. (Right) At higher magnification, the cells of metastatic NPC, nonkeratinizing undifferentiated type, include dyscohesive cells with enlarged vesicular chromatin and prominent nucleoli, findings that may erroneously suggest a diagnosis of diffuse large B-cell lymphoma.

Metastatic NPC, Nonkeratinizing Undifferentiated Type, Cytokeratin (+)



Metastatic NPC, Nonkeratinizing Undifferentiated Type, EBER(+)



(Left) The metastatic neoplastic cells are diffusely and strongly immunoreactive for cytokeratin, confirming the diagnosis of metastatic carcinoma and allowing differentiation from diffuse large B-cell lymphoma. (Right) Metastatic NPC, nonkeratinizing undifferentiated type, demonstrates the presence of in situ hybridization for EBER, confirming the metastasis as originating from the nasopharynx.

KEY FACTS

TERMINOLOGY

- Type of squamous cell carcinoma originating from nasopharyngeal mucosa showing evidence of squamous differentiation

ETIOLOGY/PATHOGENESIS

- Nasopharyngeal carcinoma (NPC), keratinizing type, not considered to be associated with EBV or HPV

CLINICAL ISSUES

- Represents ~ 25% of all NPC
- Represents ~ 25% of all NPC
- Lateral wall > superior posterior wall
- Supervoltage radiotherapy treatment of choice
- Overall 5-year survival: 20-40%
- Higher incidence of locally advanced tumor, but lower incidence of lymphatic &/or distant spread
- Poorer 5-year survival rate due to higher incidence of deaths secondary to local uncontrollable disease

MICROSCOPIC

- Infiltrative carcinoma characterized by presence of keratinization and intercellular bridges
- Graded as well, moderately, or poorly differentiated
- Stromal desmoplasia is present
- Relative absence of associated lymphoid cell infiltrate

ANCILLARY TESTS

- Consistent strong staining for cytokeratins, p63
- **Negative:** p16
- Molecular studies for EBV-encoded RNA
 - Positive in endemic areas, generally negative in nonendemic areas

Infiltrative Carcinoma With Desmoplasia

(Left) Invasive, well-differentiated, keratinizing squamous cell carcinoma invades into the submucosa with associated desmoplastic stromal reaction and invasion into skeletal muscle [A].

(Right) Invasive, well-differentiated, keratinizing squamous cell carcinoma is characterized by the presence of limited (mild) cytologic atypia, cells with identifiable keratinization [B], and intercellular bridges [C].

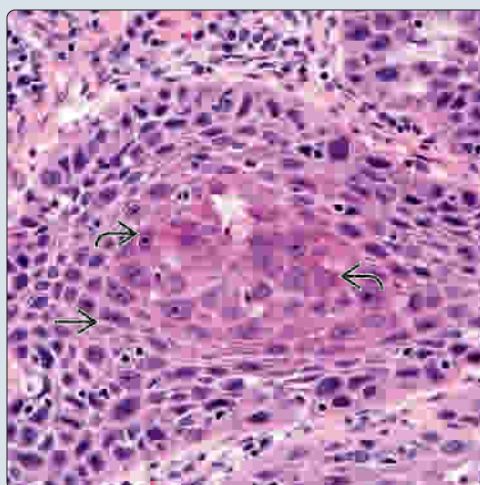


Well-Differentiated Squamous Cell Carcinoma

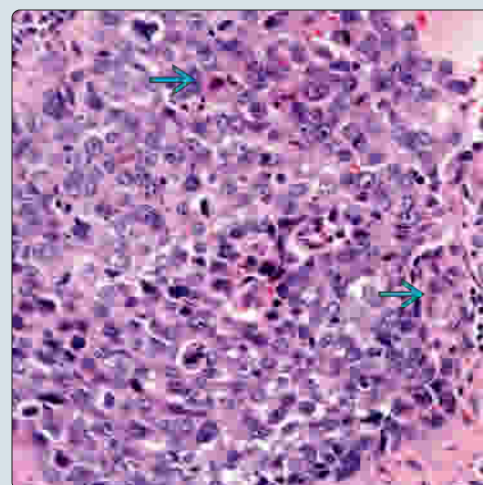


Moderately Differentiated Squamous Cell Carcinoma

(Left) Invasive, moderately differentiated, keratinizing squamous cell carcinoma with greater nuclear pleomorphism than well-differentiated carcinoma and less, but still recognizable, squamous differentiation including keratinization [A] and intercellular bridges [B] is shown. **(Right)** Invasive, poorly differentiated squamous cell carcinoma shows less squamous differentiation as compared to better differentiated carcinomas, although keratinization is present [C], which is indicative of squamous carcinoma.



Poorly Differentiated Squamous Cell Carcinoma



TERMINOLOGY

Abbreviations

- Nasopharyngeal carcinoma (NPC)

Definitions

- Type of squamous cell carcinoma originating from nasopharyngeal mucosa showing evidence of squamous differentiation
- WHO classification of NPC
 - Keratinizing
 - Nonkeratinizing
 - Differentiated
 - Undifferentiated

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Purported risk factors include
 - Cigarette smoking
 - Occupational exposure to chemical fumes, smoke, formaldehyde
 - Prior radiation exposure
 - High dietary levels of nitrosamines in preserved food in high-incidence regions implicated as carcinogen
- NPC, keratinizing type, not considered to be associated with EBV or HPV

CLINICAL ISSUES

Epidemiology

- Incidence
 - Represents ~ 25% of all NPC
- Age
 - Most common in 4th-6th decades
 - Rarely occurs in patients under 40 years of age
- Sex
 - Male > female
- Ethnicity
 - Endemic populations include Chinese, Southeast Asians, North Africans, natives of Arctic region

Site

- Lateral wall > superior posterior wall

Presentation

- Nasal obstruction, nasal discharge, epistaxis, pain, serous otitis media, otalgia, hearing loss, headache
- Cranial nerve involvement may be present in more advanced disease

Treatment

- Surgical approaches
 - Surgical intervention reserved for patients who fail radiation therapy
- Adjuvant therapy
 - Chemotherapy integrated with radiation in advanced stage disease
- Radiation
 - Supravoltage radiotherapy (6,500 to > 7,000 rads) considered treatment of choice for all NPC histologic subtypes

Prognosis

- Overall 5-year survival: 20-40%
 - Higher incidence of locally advanced tumor, but lower incidence of lymphatic &/or distant spread
 - Poorer 5-year survival rate due to higher incidence of deaths secondary to local uncontrollable disease

IMAGING

Radiographic Findings

- Represents important diagnostic aid in assessing extent of disease and presence of metastatic disease
- MR is preferred study for detection of invasion into soft tissues, intracranial extension, and invasion into bone

MICROSCOPIC

Histologic Features

- Infiltrative carcinoma characterized by presence of keratinization and intercellular bridges
 - Graded as well, moderately, or poorly differentiated
- Stromal desmoplasia is present
- Relative absence of associated lymphoid cell infiltrate

ANCILLARY TESTS

Immunohistochemistry

- Consistent strong staining for cytokeratins, p63
- **Negative:** p16

Genetic Testing

- Molecular studies for EBV-encoded RNA
 - Positive in endemic areas, generally negative in nonendemic areas

DIFFERENTIAL DIAGNOSIS

Reactive Epithelial Hyperplasia

- May show reactive atypia but lack:
 - Significant dysplastic epithelial changes, invasive tumor

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KEY FACTS

TERMINOLOGY

- High-grade variant of squamous cell carcinoma (SCC) histologically characterized by invasive neoplasm composed predominantly of basaloid pleomorphic cells and variable squamous component

ETIOLOGY/PATHOGENESIS

- Etiologic factors of basaloid squamous cell carcinoma (BSCC) occurring in more common sites include excessive alcohol &/or tobacco use
- Likely not Epstein-Barr virus (EBV) associated; presence of EBV endemic to Asian population
- Nasopharyngeal BSCC typically not associated with HPV

CLINICAL ISSUES

- Uncommon type of primary nasopharyngeal carcinoma
- Radical surgical excision
- Neck dissection, radiotherapy and chemotherapy may be included in initial management

- Disease specific survival better than BSCC of larynx but worse than BSCC of oropharynx

MICROSCOPIC

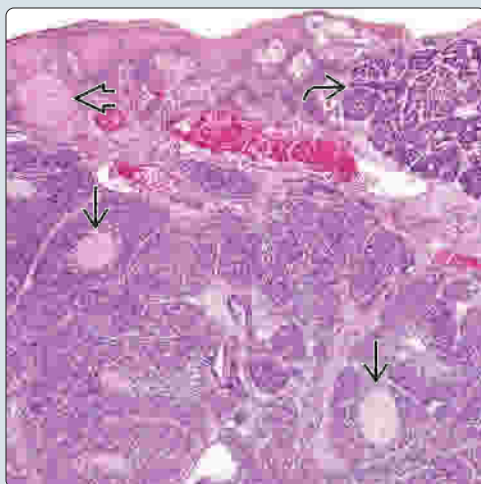
- Varied growth patterns, including lobular (\pm comedonecrosis), solid, trabecular
- Basaloid cell component is predominant cell type characterized by pleomorphic, hyperchromatic nuclei with increased mitotic activity
- Squamous cell component typically represents minor component, including keratinization, invasive SCC
- Tends to be deeply invasive at presentation, including neurotropism and lymph-vascular invasion

ANCILLARY TESTS

- Strong immunoreactivity for cytokeratins (AE1/3, CAM5.2, CK5/6), p63
- Neuroendocrine markers usually negative but occasionally may be positive

Diffusely Infiltrative Tumor

(Left) Irrespective of its site of origin, the histologic features of BSCC are similar, including the presence of infiltrative basaloid cell neoplasm with varied growth, including lobular and trabecular patterns; abrupt squamous differentiation is present. Comedo-type necrosis is present in center of the lobules. (Right) In addition to keratinization or invasive squamous cell carcinoma, there may be intraepithelial dysplasia or carcinoma in situ, a feature supporting origin from the overlying surface epithelium.

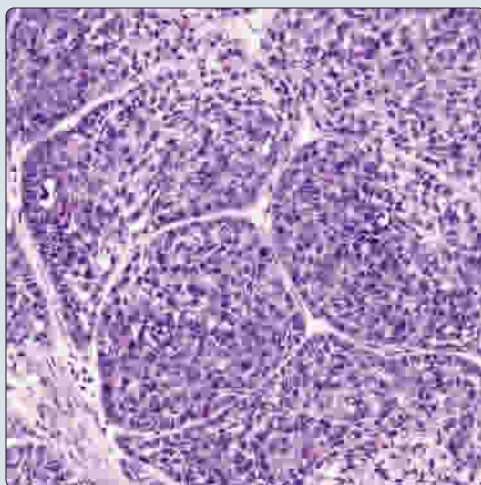


Carcinoma In Situ Component

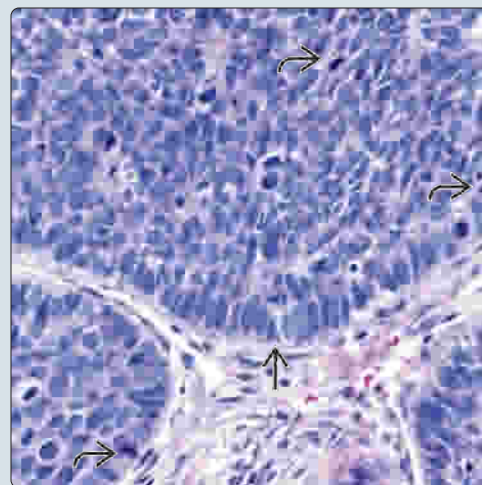


Malignant Basaloid Cells With Lobular Growth

(Left) Infiltrative nests or lobules show a jigsaw puzzle-like configuration and are predominantly composed of malignant basaloid cells characterized by marked nuclear pleomorphism. In this image, squamous differentiation is not identified. (Right) At higher magnification, the basaloid cells show marked nuclear pleomorphism and hyperchromasia, and increased mitotic activity. Peripheral nuclear palisading is present but retraction artifact from the surrounding stroma is not present.



Nuclear Pleomorphism and Mitoses



TERMINOLOGY

Abbreviations

- Basaloid squamous cell carcinoma (BSCC)

Definitions

- High-grade variant of squamous cell carcinoma histologically characterized by invasive neoplasm composed predominantly of basaloid pleomorphic cells and variable squamous component

ETIOLOGY/PATHOGENESIS

Alcohol and Tobacco

- Etiologic factors of BSCC occurring in more common sites include excessive alcohol &/or tobacco use

Infectious Agents

- Confusion in literature relative to association with Epstein-Barr virus (EBV)
 - Asian patients reported EBV(+), while non-Asians reported EBV(-)
 - Likely not EBV associated; presence of EBV endemic to Asian population
 - Nasopharyngeal BSCC are typically not associated with human papillomavirus (HPV)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon type of primary nasopharyngeal carcinoma
 - In other mucosal sites of upper aerodigestive tract, majority predilect to hypopharynx (piriform sinus), larynx (supraglottis), and palatine tonsil
- Age
 - Occurs over wide age range from 3rd-8th decades of life (mean: 55 years)
- Sex
 - Male > female

Presentation

- Symptoms depend on site of occurrence
 - Nasopharyngeal tumors may present with dysphagia, epistaxis, or adenopathy

Treatment

- Options, risks, complications
 - Radical surgical excision
 - Due to early regional lymph node as well as distant visceral metastases, radical neck dissection, supplemental radiotherapy, and chemotherapy may be included in initial management protocol

Prognosis

- Nasopharyngeal BSCCs appear to have lower clinical aggressiveness compared to BSCC of other head and neck sites
- Disease-specific survival for nasopharyngeal BSCC better than BSCC of larynx but worse than BSCC of oropharynx
- In general, BSCCs of more common head and neck sites (except oropharynx) are aggressive, high-grade tumors with increased tendency to be multifocal, deeply invasive, and metastatic

- Metastases occur via lymphatics and blood vessels with sites of predilection, including regional and distant lymph nodes, lung, bone, skin, and brain
- Metastases include both basaloid and squamous cell components
- Rapidly fatal associated with high mortality rates within 1st year following diagnosis

MACROSCOPIC

General Features

- Firm to hard, tan-white mass often with associated central necrosis
- Infrequently may be exophytic in appearance

Size

- May reach large size, measuring up to 6 cm in greatest dimension

MICROSCOPIC

Histologic Features

- Morphologically similar to BSCC of other (more common) head and neck sites
- Invasive neoplasm predominantly composed of basaloid cells with associated squamous component
 - Varied growth patterns, including solid, lobular, cribriform, cords, trabeculae, and gland-like or cystic
 - Tends to be deeply invasive at presentation, including neurotropism and lymph-vascular invasion
 - Shallow biopsies may belie depth and extent of invasion
- Basaloid cell component
 - Predominant cell type
 - May be seen in direct continuity with surface epithelium
 - Pleomorphic, hyperchromatic nuclei, scanty cytoplasm, and variably sized, but identifiable, nucleoli
 - Peripheral nuclear palisading may be present
 - Increased mitotic activity, including atypical mitoses
 - Necrosis commonly seen, including comedonecrosis seen in center of neoplastic lobules
 - Comedonecrosis seen in center of neoplastic lobules
 - Individual cell necrosis
 - Intercellular deposition of hyaline or mucohyaline material can be seen
 - Similar in appearance to reduplicated basement membrane material seen in some salivary gland tumors
 - Additional findings may include
 - Cells with clear-appearing cytoplasm may be seen either focally or more extensively
 - Spindle cell component may be identified but usually very focal, not predominate cell type
 - Infrequently, true neural-type rosettes may be present
 - Calcifications may be present
- Squamous cell component
 - Typically, represents minor component
 - May only be focally present
 - In biopsies, squamous cell component may be absent

- Includes intraepithelial dysplasia (moderate to severe dysplasia) &/or invasive squamous cell carcinoma ± foci of abrupt keratinization
- Continuity with surface epithelium may be present

ANCILLARY TESTS

Histochemistry

- Diastase-sensitive, periodic acid-Schiff (+) intracytoplasmic material indicative of glycogen may be present especially in cells with clear cytoplasm

Immunohistochemistry

- Strong and diffuse immunoreactivity for epithelial markers, including cytokeratins (e.g., AE1/3, CAM5.2, CK5/6) and p63
- Neuroendocrine markers, including chromogranin, synaptophysin, CD56 usually negative but occasionally may be positive (synaptophysin > chromogranin) but tend to be focal
- Variable expression seen for vimentin, NSE, S100 protein, actin
- Likely EBV(-), although, discrepant results reported
- p16(-)
 - Oropharyngeal (tonsil, base of tongue) BSCC often are p16(+)
 - Nonoropharyngeal BSCCs mostly p16(-)
- Melanocytic markers and hematology markers (-)

Electron Microscopy

- Cell groups with numerous and prominent tonofilament bundles, increased desmosomes, epithelial pearls, loose stellate granules, or replicated basal lamina within cystic spaces
- Absence of glandular differentiation

DIFFERENTIAL DIAGNOSIS

Oropharyngeal Nonkeratinizing (Human Papillomavirus-Associated) Carcinoma

- May share overlapping histologic features with BSCC
- Cells are
 - Nonkeratinizing, characterized by pleomorphic, basaloid-appearing nuclei with increased mitotic activity
- Squamous cell differentiation (keratinization) may be seen
- Immunoreactive for p16 (diffuse and strong nuclear and cytoplasmic staining in >70-75% of cells)
- Presence of transcriptionally active HPV confirmed by molecular analysis (e.g., PCR, ISH)

Adenoid Cystic Carcinoma

- Uncommon nasopharyngeal cancer but among one of the more common types of malignant salivary gland neoplasms of this location
- Characterized by
 - Cribriform growth that may include other growth patterns, such as tubular/glandular and solid
 - Cytomorphologic features include the presence of
 - Isomorphic hyperchromatic basaloid cells lacking pleomorphism, mitotic activity, and necrosis
- Squamous differentiation not a finding seen in association with adenoid cystic carcinoma

- Presence of squamous differentiation in a given tumor should raise suspicion against diagnosis of adenoid cystic carcinoma even in presence of cribriform growth
- Immunohistochemical staining not helpful in differential diagnosis
- Presence of balanced translocation resulting in the *MYB-NFIB* fusion gene is characteristically present in adenoid cystic carcinoma

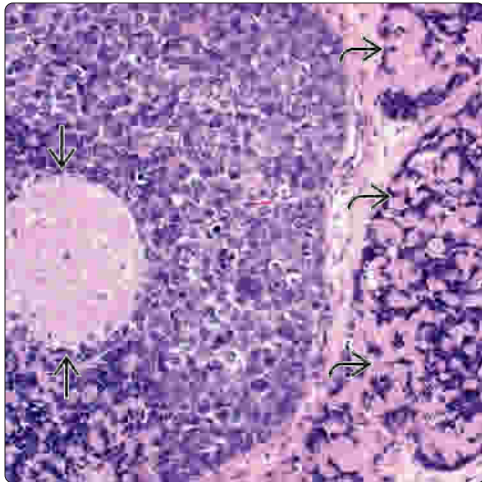
Small Cell Undifferentiated Neuroendocrine Carcinoma

- Neoplastic cells composed of small nuclei with dispersed (stippled appearing) nuclear chromatin with increased mitotic activity and necrosis (confluent foci and individual cell)
- Consistent (relatively diffuse and strong) immunoreactivity for neuroendocrine markers (chromogranin, synaptophysin, CD56)
- Typically CK5/6 and p63(-), although, positive cells may be present

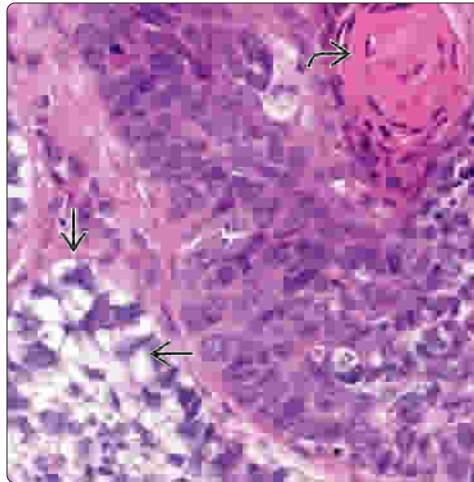
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Comedonecrosis and Reduplicated Basement Membrane Material

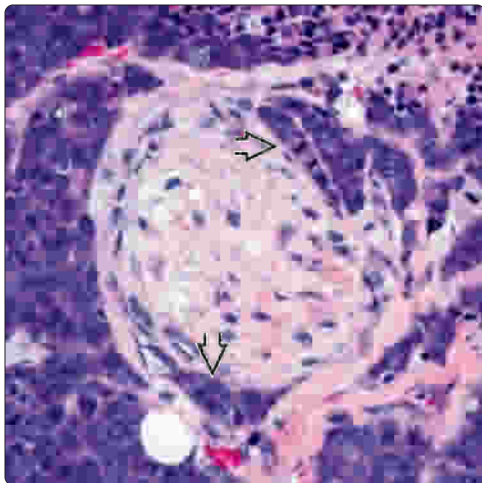


Squamous Differentiation

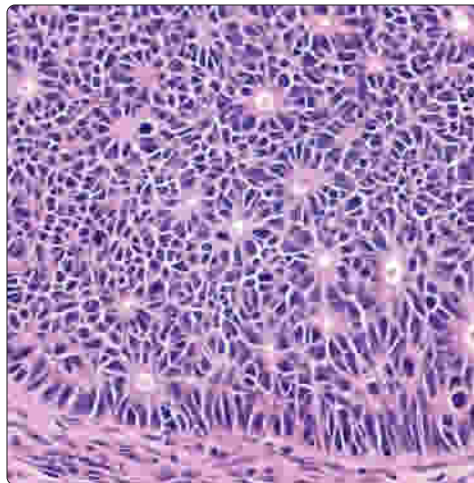


(Left) Infiltrative nest or lobule with comedo-type necrosis is shown. An adjacent area shows the presence of reduplicated basement membrane-like material reminiscent of basaloid-type salivary gland tumors (adenoid cystic carcinoma and basal cell adenocarcinoma). (Right) The squamous differentiated component represents the minor component and may appear as limited foci of abrupt keratinization. Additional cell types that can be seen in BSCC include clear cells that by PAS-D staining contain glycogen (not shown).

Neurotropism

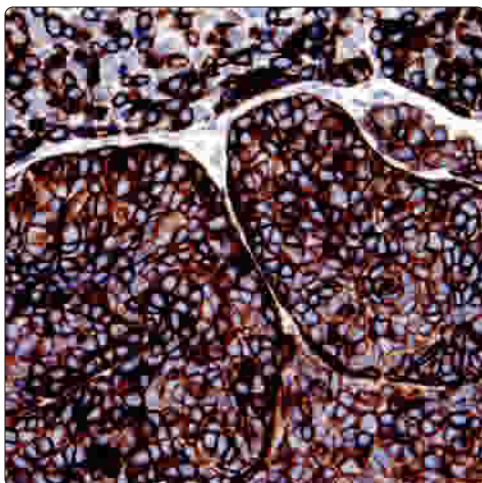


Neural-Type Rosettes

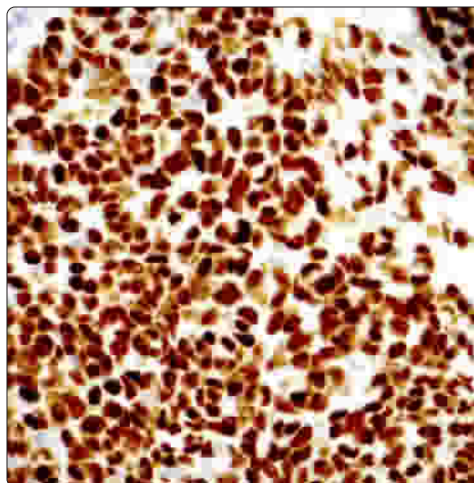


(Left) Perineural invasion with lesional cells intimately associated with the perineurium of a small nerve is a common, although not pathognomonic, feature seen in association with BSCC. (Right) Neural-type rosettes can be seen in BSCC that, in conjunction with dispersed nuclear chromatin, raise concern for a possible diagnosis of poorly differentiated neuroendocrine carcinoma (NEC). Immunostaining normally allows for differentiating BSCC from NEC.

Cytokeratin Immunoreactivity



p63 Immunoreactivity



(Left) Diffuse and strong immunoreactivity for cytokeratin 5/6 is shown. (Right) Diffuse and strong (nuclear) immunoreactivity for p63 is shown. While BSCCs may show focal staining with chromogranin or synaptophysin suggesting a possible diagnosis of NEC, the presence of diffuse CK5/6 and p63 are not usually present in NEC but rather are typically present in BSCC, which should allow for differentiating these tumor types.

KEY FACTS

TERMINOLOGY

- Surface epithelial-derived malignant tumor with adenocarcinomatous differentiation and indolent biologic behavior

ETIOLOGY/PATHOGENESIS

- No known etiologic factors

CLINICAL ISSUES

- Rare primary tumor of nasopharynx
- Occurs 2nd-7th decades (median: 37 years)
- Most common in posterior and lateral nasopharyngeal walls and roof
- Nasal obstruction most common symptom
- Complete surgical excision (treatment of choice) is curative

MICROSCOPIC

- Unencapsulated and infiltrative tumor composed of papillary and glandular growth patterns

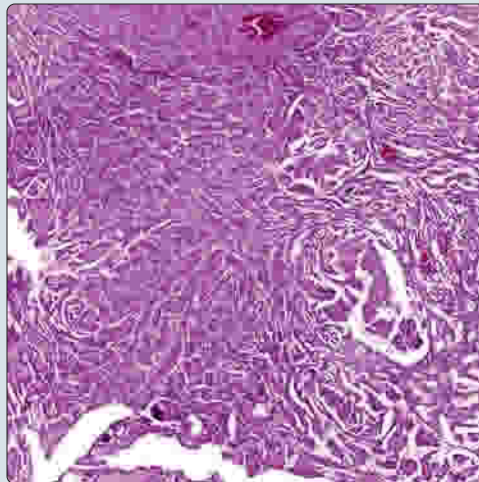
- Papillae are complex; arborization with fibrovascular cores
- Complex glandular pattern with back-to-back and cribriform growth
- Transition from surface epithelium to neoplastic proliferation supports surface epithelial derivation
- Round to oval nuclei with vesicular to optically clear chromatin
- Psammoma bodies can be identified
- Mild to moderate nuclear pleomorphism may be present
- Mitoses, prominent nucleoli, and necrosis uncommon

ANCILLARY TESTS

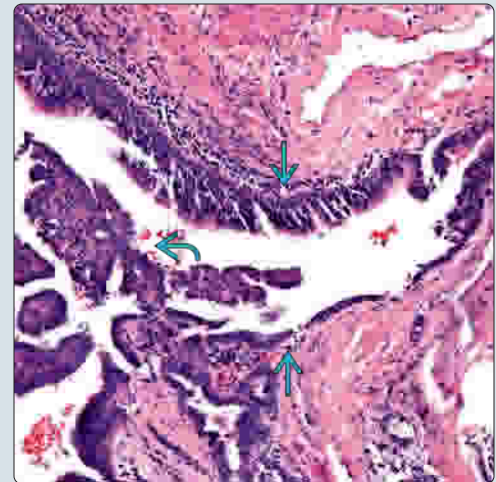
- Cytokeratins and epithelial membrane antigen diffusely **positive**
- TTF-1 **positivity** (nuclear staining)
 - **Negative:** Thyroglobulin
- Low proliferation indices by Ki-67 of < 5%

Papillary and Glandular Growth

(Left) Infiltrating tumor with complex papillary and glandular growth is characteristically seen. Such an appearance, even at low magnification, suggests a malignant neoplasm. **(Right)** The presence of transitional areas from normal surface epithelium to the neoplastic proliferation confirms origin from the nasopharyngeal surface epithelium and generally excludes alternative diagnoses, such as a salivary gland neoplasm or metastatic papillary thyroid carcinoma.

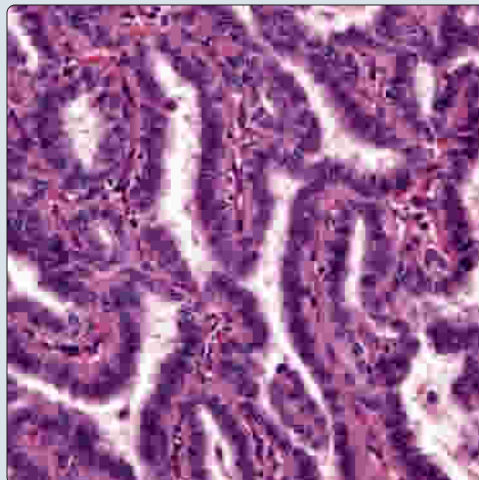


Transitional Area

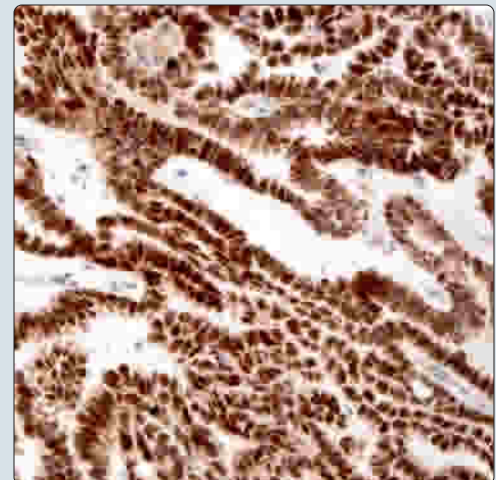


Papillary Architecture and Nuclear Features

(Left) Papillary growth and fibrovascular cores are seen composed of pseudostratified columnar to cuboidal cells with enlarged nuclei that are crowded or overlap and have dispersed to clear-appearing chromatin. The nuclear features are reminiscent of papillary thyroid carcinoma. Further, psammoma bodies may be present (not shown). **(Right)** TTF-1 immunoreactivity (nuclear staining) is consistently present, but thyroglobulin staining is absent.



TTF-1 Immunoreactivity



TERMINOLOGY

Synonyms

- Thyroid-like, low-grade nasopharyngeal papillary adenocarcinoma

Definitions

- Surface epithelial-derived malignant tumor with adenocarcinomatous differentiation and indolent biologic behavior

ETIOLOGY/PATHOGENESIS

Idiopathic

- No known etiologic factors
- No association with infectious agents (e.g., Epstein-Barr virus, human papillomavirus, others)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare primary tumor of nasopharynx
- Age
 - Occurs over wide age range: 2nd-7th decades (median: 37 years)
- Sex
 - Equal gender distribution

Site

- May occur anywhere in nasopharynx but is most common in posterior and lateral nasopharyngeal walls and roof

Presentation

- Nasal obstruction most common symptom
 - Otitis media ± associated hearing deficits and postnasal drip may be present

Treatment

- Options, risks, complications
 - Complete surgical excision is treatment of choice
- Radiation
 - Radiotherapy (pre- and postoperative) not warranted

Prognosis

- Cured by surgical resection
- Slow-growing tumor with potential to recur if incompletely excised
- Metastatic disease does not occur

MACROSCOPIC

General Features

- Exophytic, soft to gritty mass with papillary, nodular, and cauliflower-like appearance

MICROSCOPIC

Histologic Features

- Unencapsulated and infiltrative tumor composed of papillary and glandular growth patterns
 - Papillae are complex; arborization with fibrovascular cores

- Complex glandular pattern with back-to-back and cribriform growth
- Transition from normal nasopharyngeal surface epithelium to neoplastic proliferation
- Cells vary in appearance from pseudostratified columnar to cuboidal
 - Nuclei are round to oval with vesicular to optically clear-appearing chromatin
 - Nuclear crowding and overlapping with loss of basal polarity
 - Nuclear (pseudo)inclusions not typically seen
 - Psammoma bodies can be identified
- Mild to moderate nuclear pleomorphism may be present
- Mitoses, prominent nucleoli, and necrosis not commonly identified

ANCILLARY TESTS

Histochemistry

- Epithelial mucin material present
 - Intracytoplasmic and intraluminal mucicarmine and PAS-D(+) material

Immunohistochemistry

- Cytokeratins and epithelial membrane antigen diffusely **positive**
- TTF-1 **positivity** (nuclear staining)
 - **Negative:** Thyroglobulin
- CEA focally reactive
- **Negative:** S100 protein, GFAP
- Low proliferation indices by Ki-67 of < 5%

DIFFERENTIAL DIAGNOSIS

Papilloma (Surface Epithelial or Minor Salivary Gland Origin)

- Exophytic lesion lacking complex (back-to-back) growth and infiltrative pattern of nasopharyngeal papillary adenocarcinoma

Minor Salivary Gland Neoplasms

- Differentiation based on surface epithelial origin, complex papillary growth, cytomorphic features, TTF-1 reactivity

Metastatic Papillary Thyroid Carcinoma

- Both tumor types are TTF-1(+) but thyroglobulin only positive in papillary thyroid carcinoma

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KEY FACTS

TERMINOLOGY

- Primary malignant hematolymphoid neoplasm with bulk of disease occurring in Waldeyer ring representing group of extranodal lymphoid tissues, including palatine tonsils, nasopharyngeal tonsils (adenoids), base of tongue/lingual tonsils

ETIOLOGY/PATHOGENESIS

- No known etiology in majority of patients

CLINICAL ISSUES

- Diffuse large B-cell lymphoma (DLBCL) is most common non-Hodgkin lymphoma of Waldeyer ring
- Majority (~ 80%) are primary to the site of involvement
- Most common in tonsils > nasopharynx > base of tongue
- Majority (80%) are localized disease/low clinical stage (i.e., stage IE, IIE)
- Treatment includes chemotherapy and radiotherapy

- Overall 10-year disease-free survival (for all treatment modalities) ~ 66%; overall survival rate: 82%



MICROSCOPIC

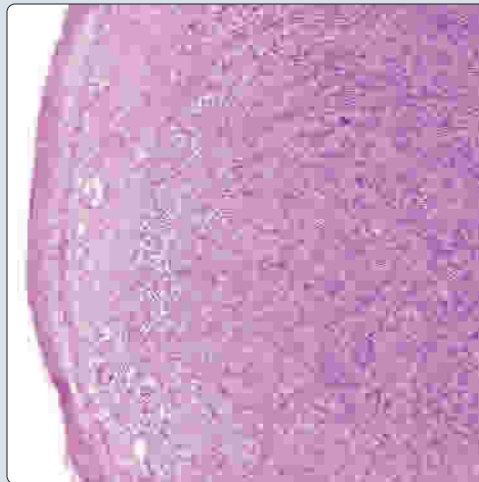
- Diffuse submucosal dyscohesive cellular infiltrate with effacement of normal architecture, including absence/loss of germinal centers
- Pleomorphic cells with large round to oval vesicular nuclei and prominent eosinophilic nucleoli

ANCILLARY TESTS

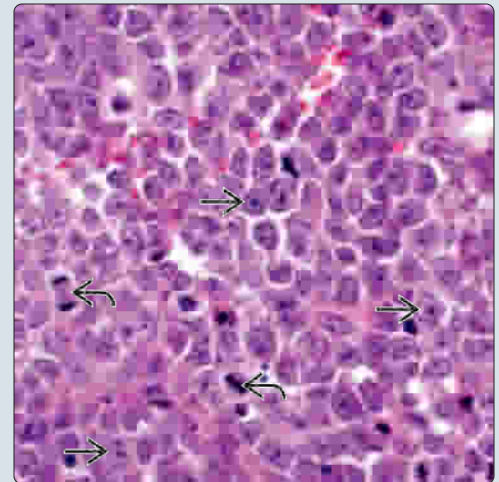
- **Positive** reactivity with CD45 and 1 or more pan-B cell markers, including CD20, CD79a, pax-5
- MUM1 expression (nuclear staining); Bcl-6 in ~ 60%; p63 may be **positive** (focal/scattered positive cells)
- Hans algorithm subclassifies DLBCL into germinal center B-cell type vs. non-germinal center B-cell type with very high concordance with gene expression profiling

Submucosal Diffuse Cellular Proliferation

(Left) A diffuse submucosal cellular proliferation with effacement of the normal pharyngeal mucosa is present. The surface squamous epithelium is intact and uninvolved by the submucosal cellular proliferation. **(Right)** At higher power, the dyscohesive appearing malignant (neoplastic) cells lack histologic evidence of cellular differentiation are comprised of enlarged nuclei with vesicular chromatin, prominent nucleoli , and the presence of increased mitotic activity .

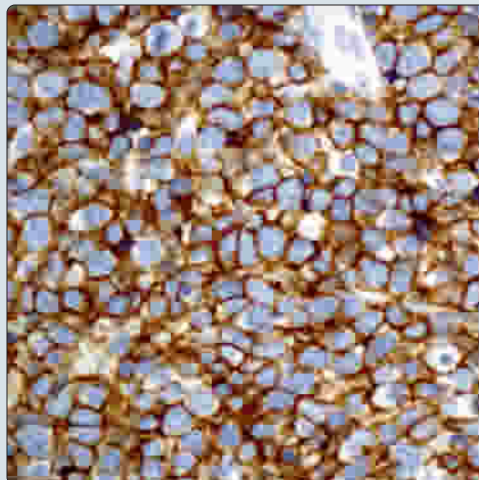


Undifferentiated Large Cells

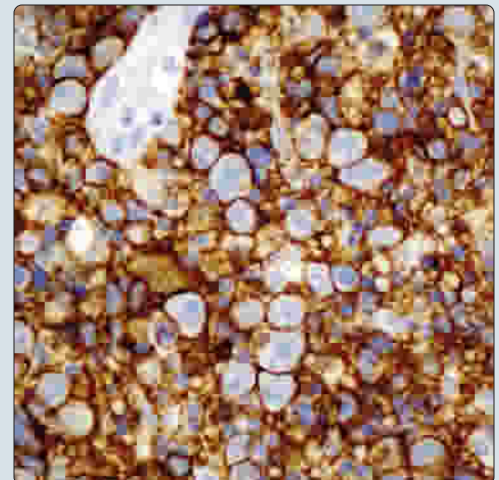


CD45 Immunoreactivity

(Left) Cytoplasmic immunoreactivity for CD45 (leukocyte common antigen) confirms a lymphoid cell origin for the neoplasm and assists in excluding other (naso)pharyngeal undifferentiated malignancy, especially an undifferentiated carcinoma. **(Right)** In addition to CD45, the lesional cells show cytoplasmic immunoreactivity for CD20, confirming their B-cell derivation. On the basis of the light microscopic features and immunohistochemical staining, a diagnosis of DLBCL can be rendered.



CD20 Immunoreactivity



TERMINOLOGY

Abbreviations

- Diffuse large B-cell lymphoma (DLBCL)

Definitions

- Primary malignant hematolymphoid neoplasm with bulk of disease occurring in Waldeyer ring
 - Group of extranodal lymphoid tissues, including palatine tonsils, nasopharyngeal tonsils (adenoids), base of tongue/lingual tonsils

ETIOLOGY/PATHOGENESIS

Idiopathic

- No known etiology in the majority of patients
- Minority of patients have underlying/associated immunodeficiency condition that may predispose to non-Hodgkin lymphoma (NHL)
 - Post-transplantation, HIV/AIDS
- Weak association of NHL, especially diffuse large B-cell lymphoma, with Epstein-Barr virus

CLINICAL ISSUES

Epidemiology

- Incidence
 - Waldeyer NHLs represent approximately
 - 5-10% of NHLs in Western countries
 - 20-25% of NHLs in Asian countries
 - 16% of all head and neck (H&N) NHLs
 - 50% of all primary H&N extranodal lymphomas
 - Any NHL type can occur, but DLBCL is most common, representing 60-84% of Waldeyer NHLs
 - Majority (~ 80%) are primary to site of involvement with minority representing secondary involvement to NHL at another site
 - Oropharyngeal NHLs account for 13% of all primary extranodal NHLs (~ 70% occur in tonsils)
 - Nasopharynx NHLs = 2.5% of all extranodal NHLs
- Age
 - Wide range but most common in 6th-8th decades of life
 - Patients with underlying immunodeficiency condition usually are younger
- Sex
 - Male > female

Site

- Tonsils > nasopharynx > base of tongue

Presentation

- Most common symptoms include dysphagia, odynophagia, swelling or lump in throat, decreased hearing, pain, and sore throat
 - Majority are unilateral (80-90% of cases)
 - Cervical adenopathy present in ~ 65% of patients
 - Systemic symptoms (e.g., fever, night sweats) not common
 - Multifocality may be present

Treatment

- Options, risks, complications

- Treatment includes multiagent chemotherapy and radiotherapy
- Surgical approaches
 - Surgical resection may be needed for symptomatic relief

Prognosis

- Majority (80%) of NHL of Waldeyer tonsillar ring present as localized disease/low clinical stage (i.e., stage IE, IIE)
- For B-cell lymphomas, including DLBCL, prognosis is dependent on clinical stage
 - Overall 10-year disease-free survival (for all treatment modalities) is ~ 66%
 - Overall survival rate of 82%
 - Relapse occurs in 30-45% of patients
- Factors associated with adverse prognosis include
 - Age of patient ≥ 60; advanced clinical stage (III or IV) (e.g., number of extranodal sites); number of extranodal sites of involvement (≥ 1); poor performance status (score of 2 or higher); abnormal serum LDH level; tumor bulk; B symptoms, including fever, drenching night sweats, loss of > 10% original weight within 6 months

MACROSCOPIC

General Features

- Often large exophytic submucosal mass ± ulceration

MICROSCOPIC

Histologic Features

- Diffuse submucosal dyscohesive cellular infiltrate with effacement of normal architecture, including absence/loss of germinal centers
 - Residual germinal centers may be identified due to incomplete involvement by lymphoma
- Neoplastic cells are composed of medium to large cells with
 - Large round to oval vesicular pleomorphic nuclei
 - Membrane-bound small nucleoli or single centrally located prominent eosinophilic nucleolus
 - Nuclear lobulation may be present
- Increased mitotic activity, including atypical forms
- Confluent (coagulative) necrosis and apoptotic figures seen
- Surface epithelium may be intact or ulcerated; crypt epithelium usually intact

ANCILLARY TESTS

Immunohistochemistry

- Waldeyer ring NHLs are predominantly follicular center cell-derived, which are positively reactive with pan-B-cell markers and negatively reactive with T-cell markers
 - **Positive** reactivity with pan-hematolymphoid marker CD45 (leukocyte common antigen [LCA]) and 1 or more pan-B cell markers, including CD20, CD79a, pax-5
 - Surface or cytoplasmic immunoglobulin **positive** (IgM > IgG > IgA)
 - Melanoma-associated antigen or multiple myeloma oncogene 1 (MUM1) expression (nuclear staining)
 - Bcl-6 in ~ 60%; CD10 expression occurs in 40%
 - CD5 and CD30 in ~ 10%
 - **Negative:** Cyclin-D1 (Bcl-1)
 - p63 may be **positive** (focal/scattered positive cells)
 - p53 **positive** in ~ 40%

Ann Arbor and AJCC Staging System for Lymphomas

Stage	Definition	Treatment	5-Year Survival
I	Involvement of a single lymphatic site (i.e., nodal region, Waldeyer ring, thymus, or spleen) (I); or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE)	Radiotherapy (4,500-5,000 rads)	50%
II	Involvement of ≥ 2 lymph node regions on the same side of the diaphragm (II); or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement \pm involvement of other lymph node regions on same side of the diaphragm (IIE)	Radiotherapy (4,500-5,000 rads)	25%
III	Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of spleen (IIIS) or both (IIIE, S)	Total lymphoid radiation; chemotherapy if the spleen is involved	17%
IV	Diffuse or disseminated involvement of ≥ 1 extralymphatic organ, \pm associated lymph node involvement; or isolated extralymphatic organ involvement in absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s)	Chemotherapy	Very poor

- **Positive:** Vimentin
- High proliferation index by Ki-67 > 20% and often > 80%
- Absence of expression for T-cell markers (CD3, others)
- Absence of epithelial, melanocytic, neuroendocrine, and myogenic markers
- **Negative:** Epstein-Barr virus testing (immunohistochemistry, in situ hybridization, others)
- Hans algorithm subclassifies DLBCL into germinal center B-cell type (GCB) vs. non-germinal center B-cell type (non-GCB) with very high concordance with gene expression profiling (GEP)
 - GCB: CD10(+), Bcl-6(+), MUM1(-)
 - Non-GCB: CD10(-), Bcl-6(+), MUM1(+)
 - GCB DLBCL purported better prognosis than non-GCB DLBCL

Genetic Testing

- Clonal rearrangement of immunoglobulin heavy and light chains genes
- Translocation of *BCL2* gene, t(14;18) occurs in 20-30%
 - t(14;18) is hallmark of follicular lymphoma
- *BCL2* and *BCL6* rearranged in ~ 20% and 30%, respectively
- *BCL6* mutation in ~ 70%
- Mutations of *TP53* in ~ 22%
- *MYC* rearranged in < 10%
 - In DLBCL, *MYC* rearrangement more frequent in HIV-infected patients and in extranodal lymphomas; usually EBV negative except in setting of immunodeficiency

DIFFERENTIAL DIAGNOSIS

Reactive Lymphoid (Follicular) Hyperplasia

- Admixture of cellular infiltrate including mature lymphocytes, plasma cells, histiocytes, others
- Retention (rather than effacement) of normal architecture including germinal centers
- Polyclonal reactivity for both B- and T-cell markers

Infectious Mononucleosis

- Histology may suggest DLBCL, but findings that allow for differentiation include

- Younger patients; preservation of germinal centers; presence of B- and T-cell markers; presence of serologic confirmation; absence of gene rearrangement

Nasopharyngeal Carcinoma, Nonkeratinizing

- **Positive:** Cytokeratins, EBER

Mucosal Malignant Melanoma

- **Positive:** S100 protein, melanocytic markers

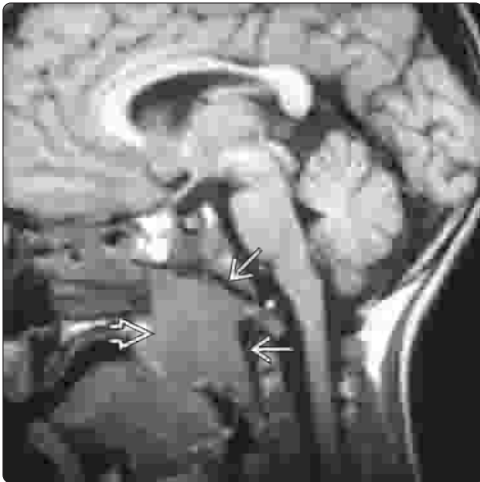
Rhabdomyosarcoma

- **Positive:** Myogenic markers

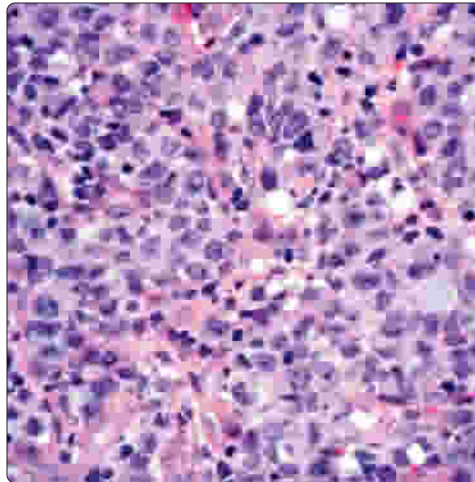
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Imaging of Pharyngeal DLBCL

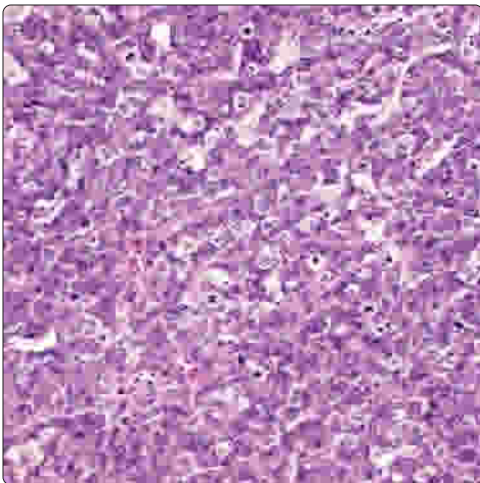


Undifferentiated Large Cell Proliferation

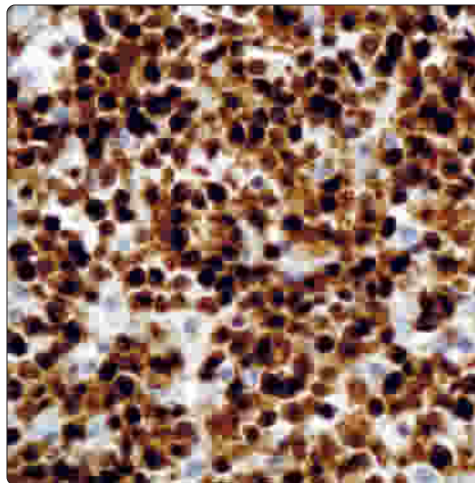


(Left) Sagittal T1 MR shows a large, retropharyngeal mass impinging on both the nasopharynx and oropharynx. This mass is isointense to muscle on T1 with some slightly lower signal intensity anteriorly. (Right) DLBCL is characterized by a diffuse population of malignant cells showing nuclear pleomorphism with vesicular nuclear chromatin and prominent eosinophilic nucleoli. These features suggest a lymphoma but requires immunohistochemical staining for confirmation.

Cohesive Growth in DLBCL

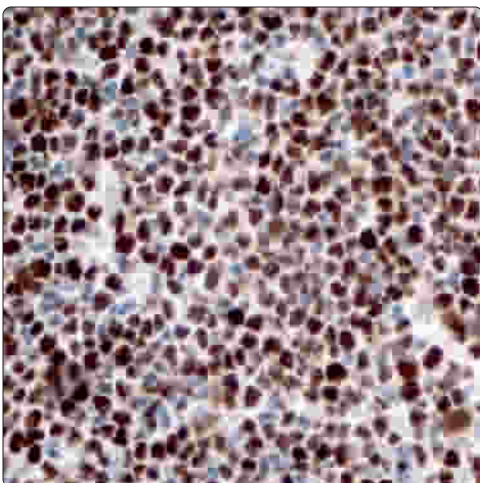


MUM1 Immunoreactivity

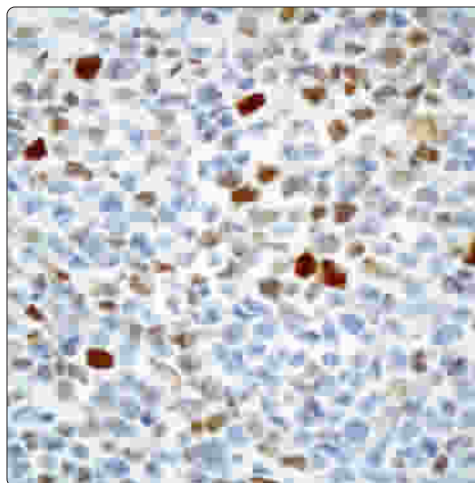


(Left) In a minority of cases, the neoplastic infiltrate in DLBCL may include a cohesive pattern of growth, a feature more commonly seen in other types of malignant neoplasms, including but not limited to carcinomas. Immunohistochemical staining showed the lesional cells to be CD45 and CD20 positive (not shown). (Right) MUM1 diffuse (nuclear) reactivity is shown. MUM1 expression can be seen in lymphomas and leukemias, and represents a marker available in the diagnosis of DLBCL.

Bcl-6 Immunoreactivity



p63 Immunoreactivity in Lymphoma



(Left) In addition to CD45, CD20, and MUM1, Bcl-6 (nuclear staining) supports the diagnosis of DLBCL being present in approximately 60% of cases. (Right) p63 (nuclear) staining can be seen in malignant lymphomas, including DLBCL. In limited tissue sampling, the presence of p63 may suggest an epithelial malignancy, as p63 is expressed in squamous and myoepithelial cells; however, the absence of markers specific for another tumor type (epithelial, melanocytic, others) should prompt consideration of a lymphoma.

PRIMARY TUMOR

Specimen

- Procedure: Excisional biopsy, resection, tonsillectomy, laryngopharyngectomy ± neck (lymph node) dissection
- Tumor site
 - Oropharynx: Palatine tonsil, base of tongue, including lingual tonsil, soft palate, uvula, pharyngeal wall
 - Nasopharynx: Nasopharyngeal tonsils (adenoids)
 - Hypopharynx: Piriform sinus, postcricoid &/or pharyngeal wall (posterior &/or lateral)
- Tumor laterality: Left, right, midline
- Tumor focality: Single focus, multifocal
- Tumor size: Greatest dimension in centimeters

Histologic Type

- Carcinomas of oropharynx and hypopharynx
 - Squamous cell carcinoma (SCC), conventional (keratinizing, nonkeratinizing)
- Variants of SCC
- Carcinomas of nasopharynx
 - Keratinizing SCC; Nonkeratinizing carcinoma (differentiated, undifferentiated); basaloid SCC
- Adenocarcinomas (non-salivary gland type)
- Carcinomas of minor salivary glands
- Neuroendocrine carcinoma; mucosal melanoma

Histologic Grade

- Well- (G1), moderately (G2), and poorly differentiated (G3)

Invasion

- Lymph-vascular invasion; perineural invasion
- Margin assessment: Uninvolved or involved by invasive carcinoma or high-grade (moderate or severe) dysplasia (include distance in mm and location per orientation)

REGIONAL LYMPH NODES

Cervical Lymph Nodes: Unilateral or Bilateral

- Oro- and hypopharynx
 - pN1: 1 ipsilateral lymph node ≤ 3 cm

- pN2: 1 ipsilateral lymph node > 3 cm but ≤ 6 cm or multiple ipsilateral lymph nodes ≤ 6 cm or bilateral or contralateral lymph nodes ≤ 6 cm
- pN3: Nodal metastasis > 6 cm
- Nasopharynx
 - pN1: Unilateral metastasis in lymph node(s) ≤ 6 cm above supraclavicular fossa
 - pN2: Bilateral metastasis in lymph node(s), ≤ 6 cm above supraclavicular fossa
 - pN3: Metastasis in lymph node > 6 cm &/or to supraclavicular fossa

PROGNOSTIC GROUPS

Oropharynx

- pT1: ≤ 2 cm; pT2: > 2 cm but ≤ 4 cm; pT3: > 4 cm or extension to lingual surface of epiglottis; pT4a: Moderately advanced local disease; pT4b: Very advanced local disease

Nasopharynx

- pT1: Confined to nasopharynx or extends to oropharynx &/or nasal cavity without parapharyngeal extension; pT2: With parapharyngeal extension; pT3: Invades bony structures of skull base &/or paranasal sinuses; pT4: With intracranial extension &/or involvement of cranial nerves, hypopharynx, orbit, or with extension to infratemporal fossa/masticator space

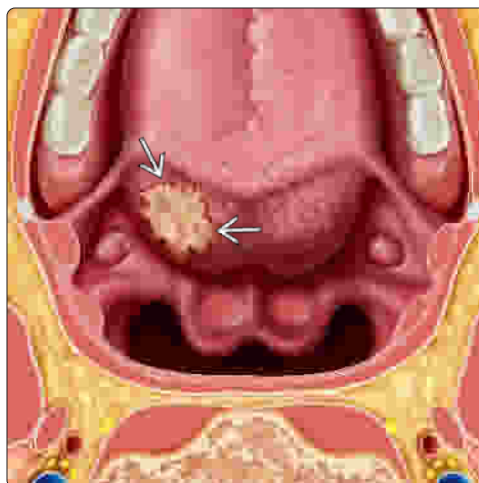
Hypopharynx

- pT1: Limited to 1 subsite of hypopharynx &/or ≤ 2 cm; pT2: Invades more than 1 subsite of hypopharynx or adjacent site, or measures > 2 cm but ≤ 4 cm without fixation of hemilarynx; pT3: > 4 cm or with fixation of hemilarynx or extension to esophagus; pT4a: Moderately advanced local disease; pT4b: Very advanced local disease

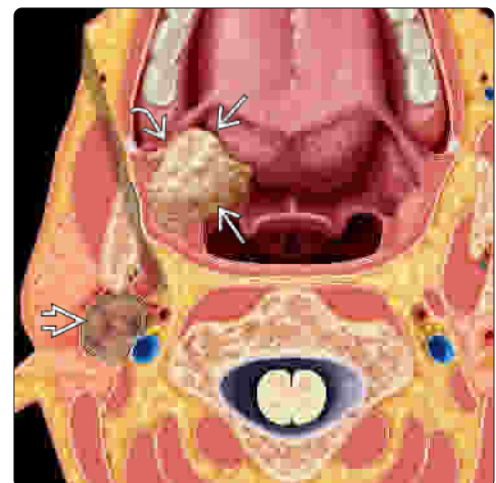
Mucosal Melanoma

- pT3: Mucosal disease; pT4a: Moderately advanced disease; pT4b: Very advanced disease; pN1: Regional lymph node metastases; pM1: Distant metastasis present

T1 Tonsil Carcinoma

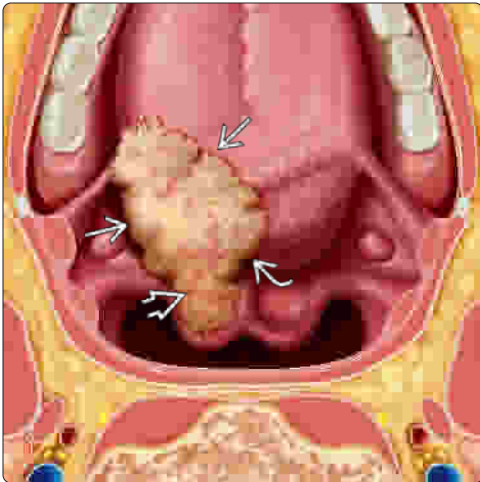


T2 Tonsil Carcinoma

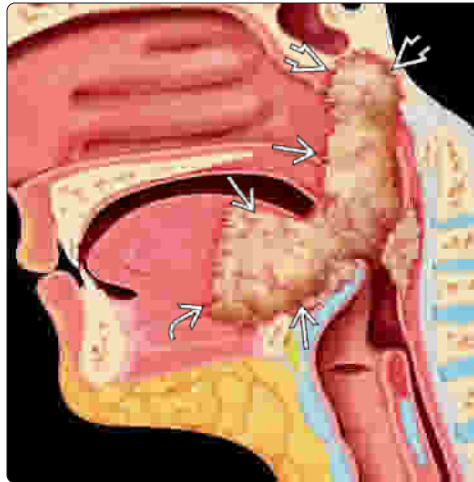


(Left) Graphic depicts a carcinoma measuring < 2 cm confined to the lingual tonsil ➡ staged as T1. Oropharyngeal carcinomas may arise from the lingual tonsil, palatine tonsillar complex, posterior oropharyngeal wall, or soft palate. (Right) Graphic illustrates large tonsil carcinoma ➡ involving the anterior tonsillar pillar ➡. The carcinoma measures < 4 cm in greatest dimension and is staged as T2. Note ipsilateral level IIA & node ➡, a frequent finding with oropharyngeal squamous cell carcinoma.

T3 Tonsil Carcinoma

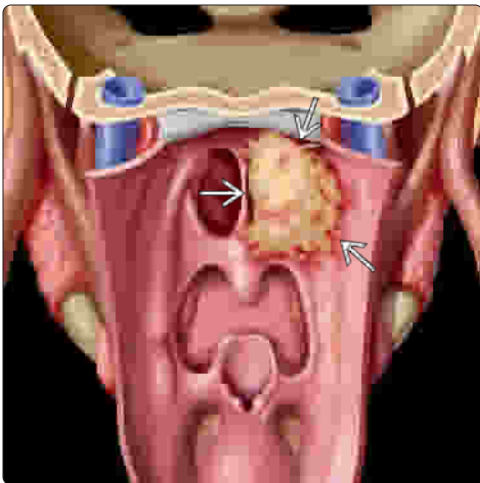


T4 Tonsil Carcinoma



(Left) Large tonsil carcinoma measures > 4 cm, staged as T3, and extends inferiorly to the vallecula. Extension to lingual surface of epiglottis is still T3 disease. Tumor extends across midline, which does not affect T staging. (Right) Very advanced local disease involves the tongue base and lateral pharyngeal wall extending anteriorly to the oral tongue and genioglossus muscle and superiorly to the skull base. Extrinsic tongue muscle involvement denotes T4a disease, but skull base invasion upstages this to a T4b tumor.

T1 Nasopharyngeal Carcinoma

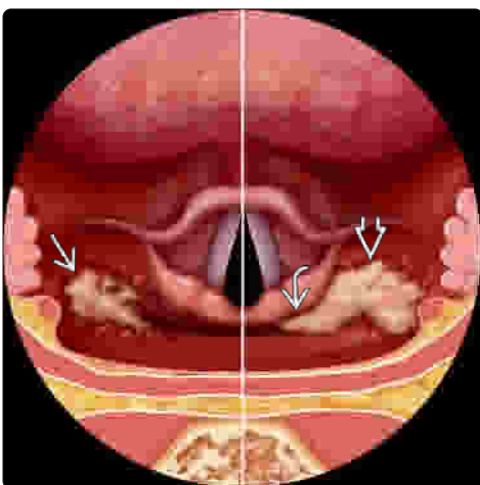


T3 Nasopharyngeal Carcinoma

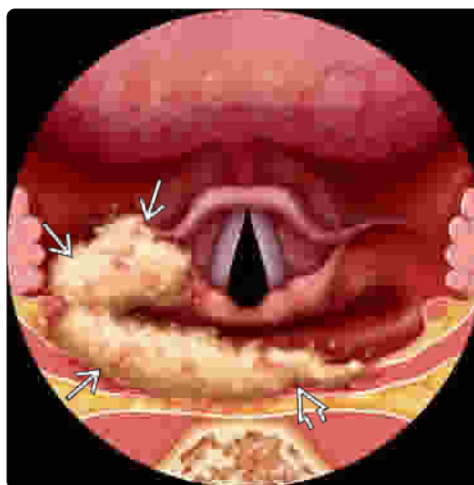


(Left) T1 NPC appears confined to the nasopharynx. A nasopharyngeal tumor may extend anteriorly to nasal cavity or inferiorly to oropharynx and still be T1 as long as there is no deep lateral infiltration to the parapharyngeal fat, which would upstage it to T2. (Right) Large NPC invades the skull base, denoting T3 disease. Involvement of the paranasal sinuses also is a T3 NPC. T4 requires involvement of the CNS, cranial nerves, hypopharynx, orbit, or extension to the masticator space/infratemporal fossa.

T1 and T2 Piriform Sinus Carcinoma



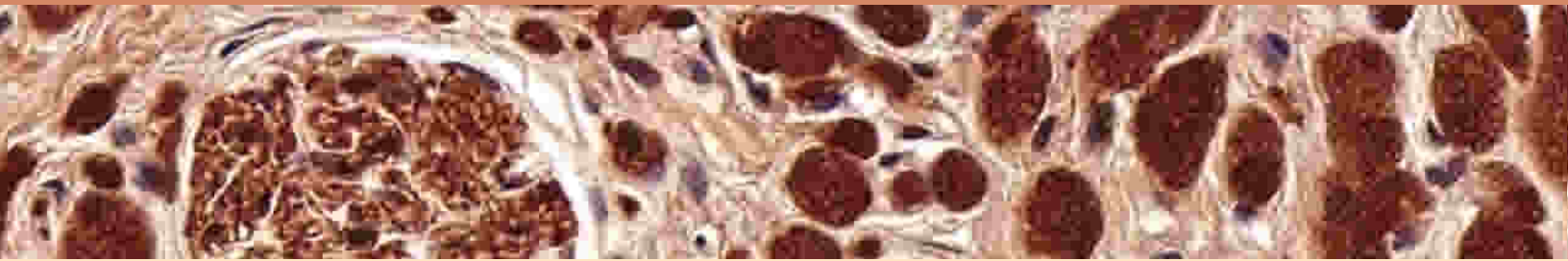
T3 Piriform Sinus Carcinoma



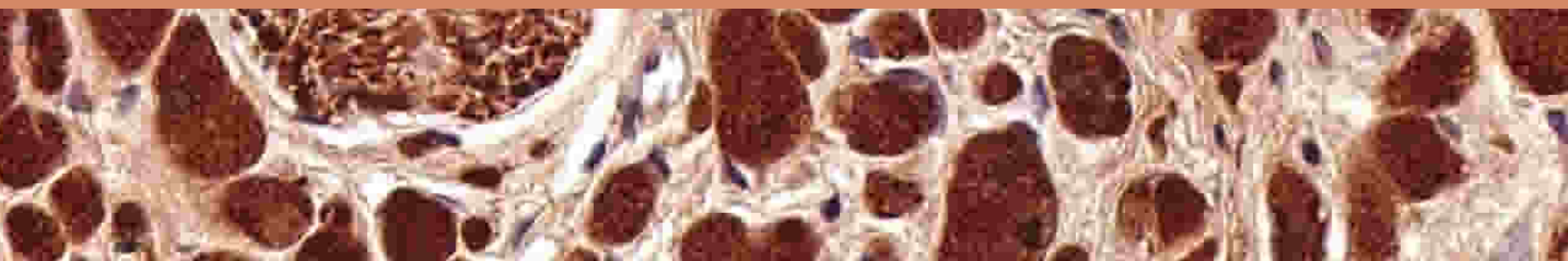
(Left) Small T1 carcinoma limited to the piriform sinus measuring < 2 cm is shown. Another carcinoma, which is larger but measuring < 4 cm, extends from the piriform sinus to the postcricoid area, upstaging it to T2. (Right) Large piriform sinus carcinoma extending medially along the posterior hypopharyngeal wall is shown. A hypopharyngeal tumor measuring > 4 cm or involving the esophagus is designated T3 disease. T4 disease requires more advanced disease extension.

SECTION 3

Larynx and Trachea



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MACROSCOPIC ANATOMY

Larynx

- Extends from the epiglottic tip superiorly to inferior border of cricoid cartilage inferiorly
 - Main functions are phonation and preventing aspiration of ingested or inhaled particles
- Composed of cartilaginous framework supported by ligaments as well as intrinsic and extrinsic muscles
 - Main cartilages are epiglottic, thyroid, cricoid, and arytenoid cartilages
- Covered by mucosa
- 3 regions: Supraglottis, glottis, subglottis
 - **Supraglottis:** Epiglottis to superior portion of true vocal cords and includes epiglottis, aryepiglottic folds, false vocal cords, and ventricles
 - Embryologically from 3rd & 4th branchial arches
 - **Glottis:** Superior portion of true vocal cords inferiorly for 1 cm and includes true vocal cords (folds), anterior commissure, and posterior commissure
 - Embryologically derived from 6th branchial arch
 - **Subglottis:** Inferior glottis to inferior border of cricoid cartilage
 - Embryologically derived from 6th branchial arch
- Anterior commissure tendon (Broyles ligament) is where the vocal cord elastic tissue attaches to thyroid cartilage
 - Represents weak point where carcinomas can spread beyond larynx
- Preepiglottic space: Adipose and loose connective tissue anterior to epiglottis
- Paraglottic space: Adipose and loose connective tissue deep to true and false vocal cords
 - Bounded by cricovocal membrane, thyroid cartilage, quadrangular membrane, and pyriform sinus
- Majority of supraglottic and glottic larynx is covered by squamous epithelium with occasional patches of ciliated columnar epithelium in supraglottis
- Superior portion of supraglottic larynx is always squamous whereas lower 1/2 is more likely to have patches of ciliated columnar epithelium
- Ventricles and subglottis are always lined by ciliated columnar epithelium
- Submucosal seromucous glands are present throughout, with exception of true vocal cords
- Submucosa of true vocal cords is loose connective tissue without lymphatics or salivary glands (Reinke space)
 - True vocal cords have band of elastic tissue (vocal ligament), which sits adjacent to vocalis (skeletal) muscle
- Epiglottis is elastic cartilage and has varying numbers of fenestrations, whereas remaining laryngeal cartilages are hyaline cartilages
 - Epiglottic fenestrations and anterior commissure are weak points where laryngeal carcinomas can spread beyond larynx

VARIATIONS

Age-Related

- At birth, larynx is lined entirely by ciliated pseudostratified respiratory mucosa
- With age, epithelium is gradually replaced by nonkeratinizing stratified squamous mucosa except for ventricle, subglottis, and rare patches in supraglottis
- Thyroid and cricoid cartilages ossify to varying degrees with age but are ossified in most adults
 - Ossification begins in 2nd-3rd decades; earlier in men
- Oncocytic metaplasia of seromucous gland ducts common > 50

Metaplasia

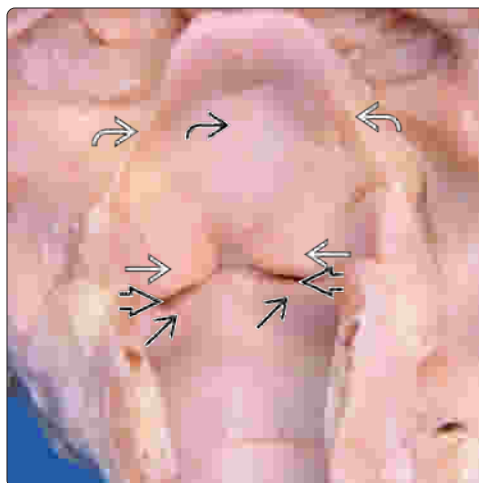
- Patients who smoke have less ciliated columnar mucosa secondary to squamous metaplasia
- Chondroid metaplasia of vocal cord ligament is not uncommon (1-2% of autopsy larynges)

MICROSCOPIC ANATOMY

Larynx

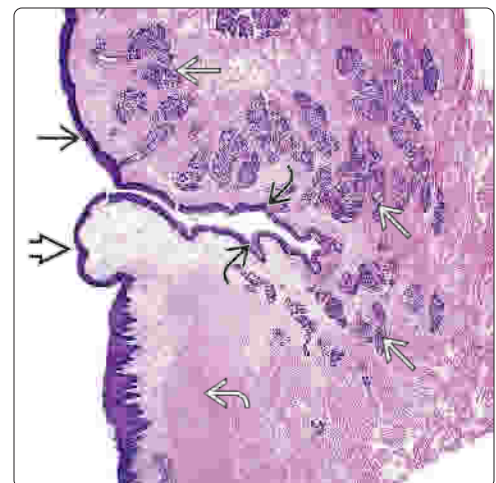
- Lined by both ciliated columnar epithelium with mucous (goblet) cells and nonkeratinized stratified squamous epithelium

Larynx Gross Anatomy

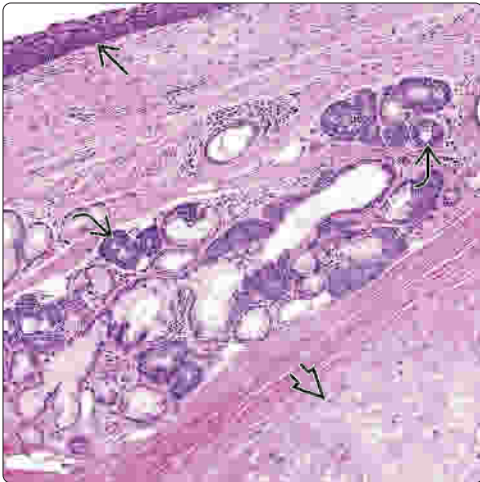


(Left) The glottis contains the true vocal cords, which are just below the ventricles. The supraglottis is also composed of the epiglottis, false vocal cords, and aryepiglottic folds. (Right) The true vocal cord with vocalis ligament is lined by squamous epithelium and is devoid of mucoserous glands. The false vocal cord is lined by squamous or respiratory epithelium and has mucoserous glands. The ventricle is lined by respiratory epithelium and also contains mucoserous glands.

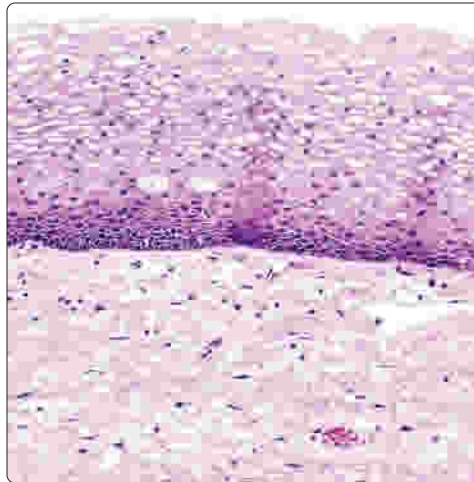
Histology of Vocal Cords



Histology of Epiglottis

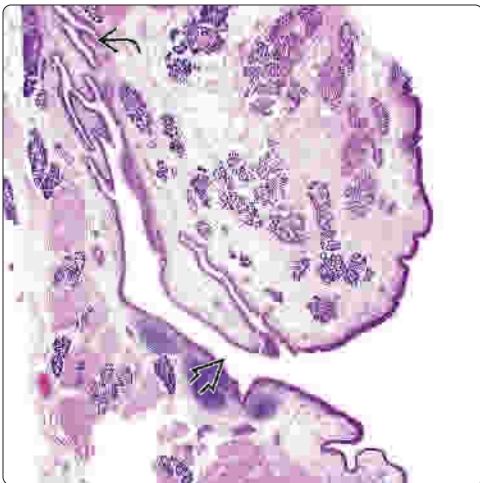


Histology of Aryepiglottic Fold

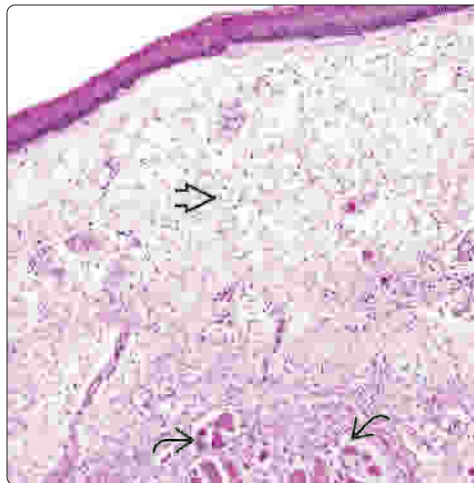


(Left) The epiglottis is lined by stratified squamous epithelium, but patches of ciliated columnar epithelium may be seen. Submucosal seromucous glands are typically found near the epiglottic cartilage. (Right) The aryepiglottic folds are part of the supraglottic larynx and extend from the epiglottis to the arytenoid cartilages. They are usually lined by stratified squamous epithelium without keratinization and have less numerous minor salivary glands in the subepithelial stroma.

Histology of Ventricle and Sacculle

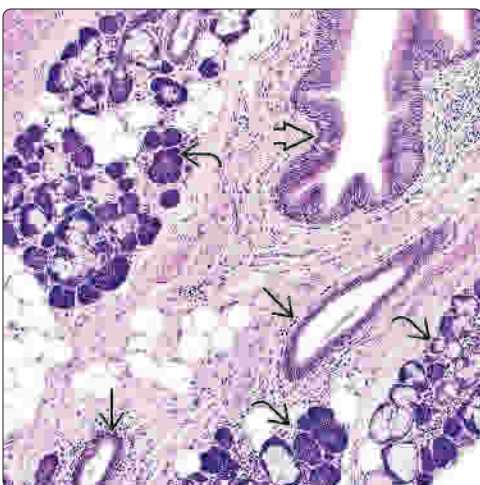


Histology of Reinke Space

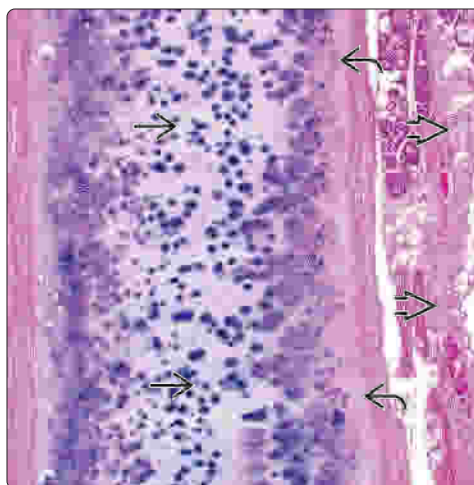


(Left) The anterior portion of the ventricle contains the sacculle, a segment that extends caudally and can result in cystic dilation if obstructed. (Right) True vocal cords contain the vocalis muscle. The lamina propria between the vocalis muscle and surface epithelium (Reinke space) contains relatively few capillaries and lacks lymphatic channels. This explains the better prognosis of low-stage glottic carcinomas and the etiology of vocal cord nodules.

Histology of the Sacculle



Thyroid Cartilage



(Left) The laryngeal sacculles represent caudal extensions of the ventricles, lined by respiratory epithelium and contain mucoserous glands that drain to the mucosal surface via small ducts. Both the sacculle and the ducts can become obstructed, leading to saccular and ductal cysts, respectively. (Right) In contrast to the epiglottis, most of the other laryngeal cartilages are composed of hyaline cartilage with an adjacent perichondrium. The paraglottic space can be seen adjacent to this thyroid cartilage.

Laryngocele and Laryngeal Cysts

KEY FACTS

TERMINOLOGY

- Synonyms
 - Saccular, ductal, oncocytic, or tonsillar cysts
- Abbreviations
 - Laryngocele (L), laryngeal cyst (LC), saccular cyst (SC), ductal cyst (DC), oncocytic cyst (OC), tonsillar cyst (TC)
- Definitions
 - Dilatation of air-filled saccule (appendix of ventricle) communicating with laryngeal lumen (L)
 - Obstruction of intramucosal ducts of seromucinous glands (DC) or laryngeal saccule without communication with laryngeal lumen (SC)

ETIOLOGY/PATHOGENESIS

- Repeated increases of intralaryngeal pressure in adults, tumors, infection, or trauma

CLINICAL ISSUES

- All ages, but most common between 50 and 60 years

MACROSCOPIC

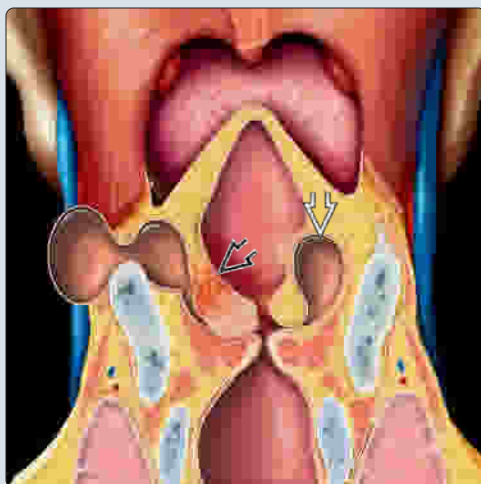
- Type of LC defines gross appearance, with internal, external, or mixed appearance

MICROSCOPIC

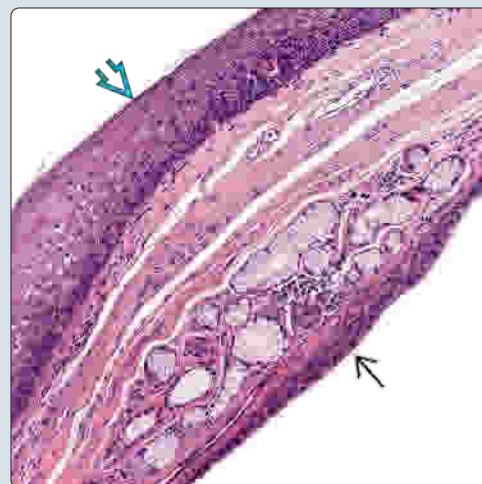
- L: Respiratory or columnar epithelium, with focal squamous or oncocytic metaplasia
- SC: Ciliated respiratory epithelium with goblet cells and partially or completely metaplastic squamous or oncocytic epithelium
- DC: Double-layered cylindrical, cuboidal, or flattened ductal epithelium with squamous or oncocytic metaplasia
- OC: Folded cystic wall with papillary infolding, double-layered: Columnar eosinophilic epithelium lining cystic lumina, with outer layer of basal cells
- TC: Cyst resembling tonsillar crypt: Squamous epithelium, keratin-filled lumen, and lymphoid tissue in wall

Graphic of Laryngoceles

(Left) This graphic demonstrates examples of an internal laryngocele (L) and an inflamed mixed internal and external laryngopyocele. In general, the histologic appearance of the lining of the space does not alter the clinical category. (Right) There is a double-layered cylindrical, cuboidal, to flattened ductal epithelium lining this ductal cyst (DC). The overlying epithelium is a squamous mucosa.

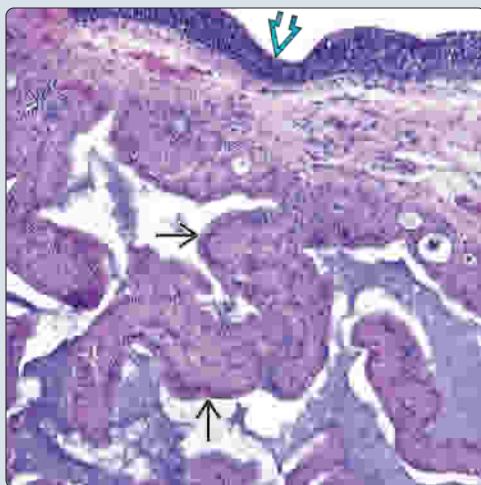


Ductal Cyst

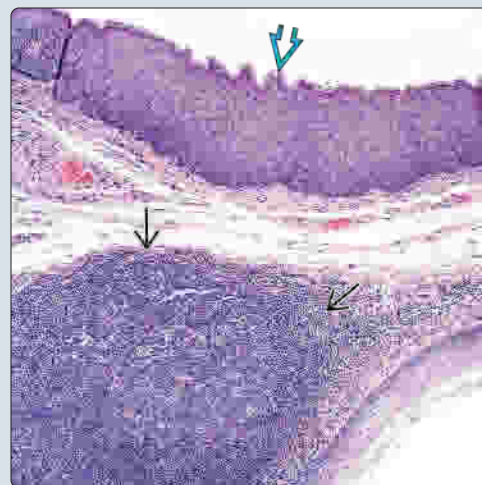


Oncocytic Cyst

(Left) The inner layer of this oncocytic cyst (OC) is composed of cylindrical eosinophilic oncocytic cells, with an outer layer lined by basal cells. The surface mucosa is respiratory epithelium. (Right) This is an example of a tonsillar cyst (TC) of the larynx in which the prominent lymphoid aggregate is noted in association with the epithelial lining of this cyst. The overlying surface epithelium is a squamous mucosa.



Tonsillar Cyst of Larynx



TERMINOLOGY

Abbreviations

- Laryngocele (L)
- Laryngeal cyst (LC)
- Saccular cyst (SC)
- Ductal cyst (DC)
- Oncocytic cyst (OC)
- Tonsillar cyst (TC)

Synonyms

- Saccular, ductal, oncocytic, or tonsillar cysts

Definitions

- Dilatation of air-filled saccule (appendix of ventricle) communicating with laryngeal lumen (L)
- Obstruction of intramucosal ducts of seromucinous glands (DC) or laryngeal saccule without communication with laryngeal lumen (SC)

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Congenital appearance of laryngocele

Environmental Exposure

- Repeated increases of intralaryngeal pressure in adults, tumors, infection, or trauma

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare (1 in 2,500,000 for laryngocele)
 - 5% of benign laryngeal lesions
 - DC are 75% and SC are 25% of all LCs
- Age
 - All ages, but most common between 50 and 60 years
- Sex
 - Male > female (L)
 - Equal gender distribution (LC)

Site

- Unilateral, internal L in laryngeal lumen (30%), external L in neck through thyrohyoid membrane (26%), mixed L with both locations (44%)
- Larynx lumen between true and false cords (SC)
- Vocal cords, ventricle of Morgagni, ventricular folds, aryepiglottic folds, and pharyngeal side of epiglottis, solitary or multiple (DC)
- Ventricle of Morgagni, ventricular folds (OC)
- Epiglottis (TC)

Presentation

- Hoarseness, cough, dyspnea, dysphagia, and foreign body sensation in internal and mixed L
- Fluctuating lateral neck mass in external L, asymptomatic L in 12% of cases
- Hoarseness, respiratory and feeding problems, foreign body sensation, and asymptomatic LC

Treatment

- Endoscopic or external surgery in symptomatic L

- Conservative treatment of LC by aspiration, marsupialization, endoscopic removal

Prognosis

- Excellent, although rarely airway obstruction and infection (laryngopyocele) or recurrences (incompletely excised LC)
- Relationship between L and laryngeal squamous cell carcinoma in up to 29% of cases

IMAGING

CT Findings

- Circumscribed, air-/fluid-filled cystic, intra- &/or extralaryngeal lesion, with possible communication

MACROSCOPIC

General Features

- Type of LC defines gross appearance, with internal, external, or mixed appearance
- Communicating (L) or noncommunicating (LC) with laryngeal lumen
- Air-filled (L), mucus, or keratin-filled

Size

- 0.5-7.5 cm

MICROSCOPIC

Histologic Features

- L
 - Respiratory or columnar epithelium, with focal squamous or oncocytic metaplasia
 - Fibrous wall with focal chronic mononuclear inflammatory cells
- SC
 - Ciliated respiratory epithelium with goblet cells and partially or completely metaplastic squamous or oncocytic epithelium
 - Fibrous wall with focal lymphocytic infiltrates
- DC
 - Double-layered cylindrical, cuboidal, or flattened ductal epithelium with squamous or oncocytic metaplasia
 - Fibrous wall, focal lymphocytic infiltrates
- OC
 - Folded cystic wall with papillary infolding, double-layered: Columnar eosinophilic epithelium lining cystic lumina, with outer layer of basal cells
- TC
 - Cyst resembling tonsillar crypt: Squamous epithelium, keratin-filled lumen, and lymphoid tissue in wall

DIFFERENTIAL DIAGNOSIS

Different Types of Cysts

- Separation between saccular, branchiogenic, dermoid, laryngocele, and teratoma based on histology

SELECTED REFERENCES

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2. Newman BH et al: Laryngeal cysts in adults: a clinicopathologic study of 20 cases. *Am J Clin Pathol.* 81(6):715-20, 1984

Tracheopathia Osteoplastica

KEY FACTS

TERMINOLOGY

- Segmental idiopathic degenerative disorder of tracheobronchial tree characterized by multiple submucosal cartilaginous and osseous nodules of various sizes narrowing upper respiratory tract

CLINICAL ISSUES

- Mean: > 50 years; range: 5-71 years
- Male > female
- Tracheobronchial tree, usually in subglottic space
- Most patients are asymptomatic (90%)
- If symptomatic: Chronic, recurrent cough, hoarseness, wheezing, stridor, dyspnea, hemoptysis, or expectoration
- Bronchoscopy considered diagnostic: Submucosal projections into laryngotracheal lumen
- Endoscopic CO₂ laser or complete linear tracheoplasty
- Disease tends to be slowly progressive

IMAGING

- Beaded or scalloped, nodular, submucosal calcified opacities of anterior and lateral walls of tracheobronchial cartilages, frequently protruding into lumen

MACROSCOPIC

- Bronchoscopy shows submucosal firm nodules

MICROSCOPIC

- Metaplastic or heterotopic cartilage and bone in submucosa
- Metaplastic or heterotopic cartilage and bone in submucosa
- Shows continuity with inner surface of tracheal cartilage
- Bone may protrude into mucosa

TOP DIFFERENTIAL DIAGNOSES

- Diffuse tracheal stenosis, relapsing polychondritis, tracheobronchomegaly, and tracheomalacia

CT of Calcified Subglottic Mucosa

(Left) Axial CECT shows diffuse calcified subglottic submucosa. Tracheopathia osteoplastica (TPO) can be thin and nonnodular or focal with discrete ossification. (Right) Multiple submucosal nodules are detected in this endoscopic view of the tracheobronchial tree. This finding is quite characteristic of the clinical setting for TPO. (Courtesy Z. Neyaz, MD.)

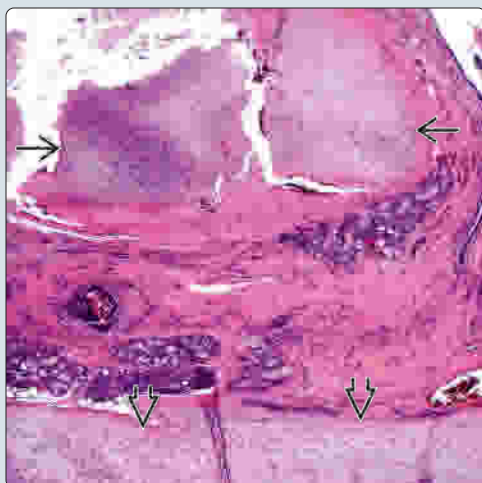


Endoscopic Image

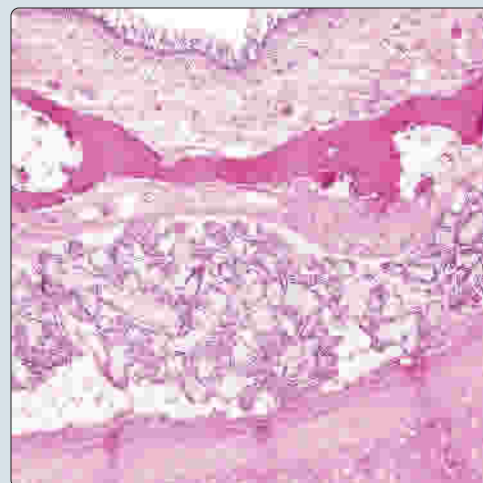


Cartilage Nodules Below Surface Mucosa

(Left) Hematoxylin & eosin shows cartilage rings with a number of nodules of cartilage immediately below the surface mucosa. The minor mucoserous glands are noted in the stroma. (Right) Hematoxylin & eosin shows calcification and bone formation below an intact respiratory-type epithelium. The minor mucoserous glands and fat separate this bone from the underlying cartilage ring.



Bony Deposits Within Stroma



TERMINOLOGY

Abbreviations

- Tracheopathia osteoplastica (TPO)

Synonyms

- Tracheopathia osteochondroplastica
- Tracheobronchopathia osteochondroplastica

Definitions

- Segmental idiopathic degenerative disorder of tracheobronchial tree characterized by multiple submucosal cartilaginous and osseous nodules of various sizes narrowing upper respiratory tract

ETIOLOGY/PATHOGENESIS

Infectious

- Persistent purulent tracheitis followed by calcium deposition, resulting in bone and cartilage forming around accumulations

Degenerative

- Nodules develop as ecchondroses of tracheal cartilage rings

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare disease in clinical practice
- Age
 - Mean: > 50 years; range: 5-71 years
 - Females older than males by about a decade
- Sex
 - Male > female

Site

- Tracheobronchial tree, usually in subglottic space

Presentation

- Most patients are asymptomatic (90%)
- If symptomatic, signs and symptoms are nonspecific, overlapping with asthma
 - Chronic, recurrent cough, hoarseness, wheezing
 - Recurrent chest infections
 - Stridor, dyspnea, breathlessness, and shortness of breath
 - Hemoptysis or expectoration
- May result in difficult intubation
- Associated with atrophic rhinitis in some cases

Endoscopic Findings

- Bronchoscopy considered diagnostic: Submucosal projections into laryngotracheal lumen

Treatment

- Options, risks, complications
 - Localized disease may not require treatment
 - Significant narrowing may require laser removal and dilatation
- Surgical approaches
 - Endoscopic CO₂ laser or complete linear tracheoplasty
 - While stents (silicone tubes) are difficult to insert, they can yield extended opening of larynx/trachea

Prognosis

- Disease tends to be slowly progressive
- Meticulous tracheobronchial hygiene is imperative for long-term clinical management
- With little morbidity or mortality, correct diagnosis prevents unnecessary operation

IMAGING

Radiographic Findings

- CT shows beaded or scalloped, nodular, submucosal calcified opacities of the anterior and lateral walls of tracheobronchial cartilages, frequently protruding into lumen
- There is sparing of posterior wall of the trachea

MACROSCOPIC

General Features

- Bronchoscopy shows submucosal firm nodules

Size

- Usually < 3-4 mm nodules studding cartilage rings

MICROSCOPIC

Histologic Features

- Metaplastic or heterotopic cartilage and bone in submucosa
- Shows continuity with inner surface of tracheal cartilage
- Bone may protrude into mucosa
- Overlying mucosa is intact and may appear normal or metaplastic
- Irregular bony spicules have thin walls surrounding fatty marrow
- Residua of inflammation (tracheitis) may be seen
- Small biopsies and lack of radiographic/bronchoscopic information make diagnosis difficult

DIFFERENTIAL DIAGNOSIS

Diffuse Tracheal Stenosis

- End-stage of multiple different diseases, lacking calcification or ossification, usually measures 2-4 cm, results in airway compromise, producing concentric or eccentric narrowing

Relapsing Polychondritis

- Mixed inflammation with destruction of cartilage from outside in; systemic disorder

Tracheobronchomegaly and Tracheomalacia

- Both disorders present with softening, flexibility, or dilatation of trachea

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2. Raess PW et al: Tracheobronchopathia osteochondroplastica presenting as a single dominant tracheal mass. Ann Diagn Pathol. 15(6):431-5, 2011
3. Penner CR et al: Tracheopathia osteoplastica. Ear Nose Throat J. 82(6):427, 2003
4. Härmä RA et al: Tracheopathia chondro-osteoplastica. A clinical study of thirty cases. Acta Otolaryngol. 84(1-2):118-23, 1977

Laryngitis: Viral, Bacterial, Fungal

KEY FACTS

TERMINOLOGY

- Different terms based on specific anatomic site affected
 - Pharyngitis, laryngitis, croup, epiglottitis
- Laryngitis can be infectious or inflammatory, acute or chronic

CLINICAL ISSUES

- Clinical manifestations depend on age, sex, nutritional and immunity status
- Thorough history, including occupation and vocal demands, may guide further evaluation
- Same organism causes different clinical disease based on age
 - Bronchiolitis in infant; croup in older child; pharyngitis in young adult; subclinical syndrome in middle-aged adult
- Croup: Hoarseness, barking cough, inspiratory stridor (noisy, labored breathing)
- Epiglottitis: Tripod sign, fever, stridor, sore throat, odynophagia, shortness of breath, drooling



- Generally, supportive measures to control symptoms
 - Culture sensitivities dictate type and duration of antimicrobial regimen

MICROSCOPIC

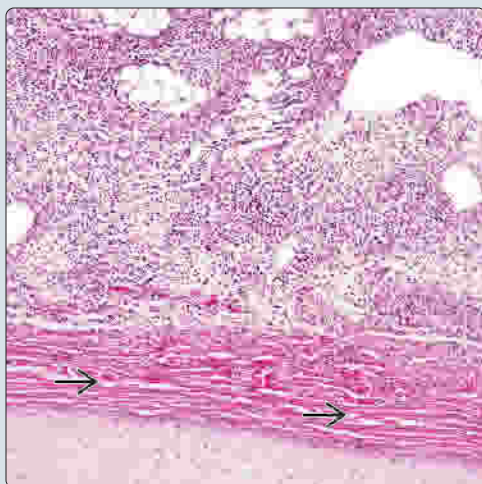
- Nonspecific inflammatory cells and edema fluid
- Surface epithelial erosion or ulceration (part of prolonged ulcerative laryngitis)
- Hyperkeratosis commonly associated with intraepithelial neutrophils
- Pseudoepitheliomatous hyperplasia associated with fungal infections

TOP DIFFERENTIAL DIAGNOSES

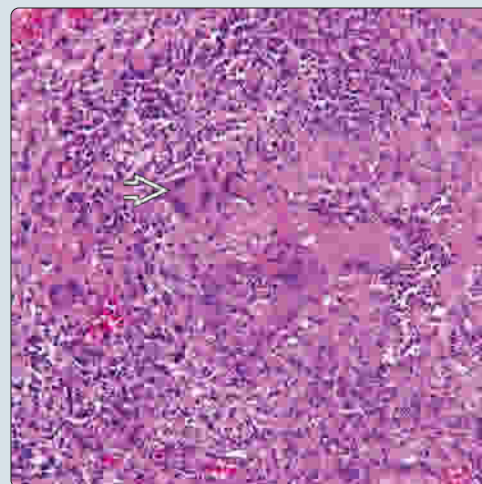
- Gastroesophageal reflux disease
- Squamous cell carcinoma (SCC)
- Wegener granulomatosis
- Relapsing polychondritis


(Left) H&E shows that the surface epithelium is lost. There is a mixed inflammatory infiltrate associated with fat and edema fluid. There is some fibrosis immediately associated with the cartilage . (Right) There are caseating granulomas associated with mixed inflammatory cells in the background, and isolated giant cells . This is from a case of tuberculosis laryngitis.

Acute Laryngitis

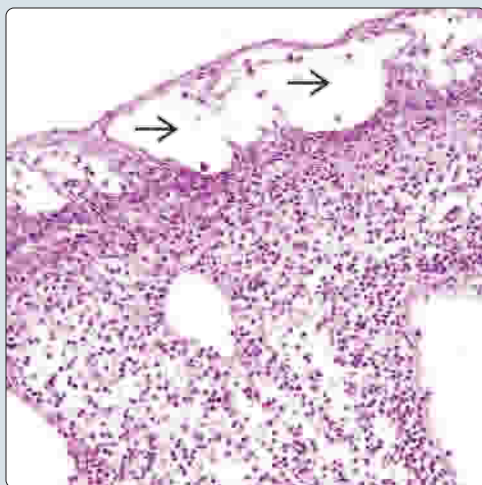


Caseating Granuloma in Tuberculosis

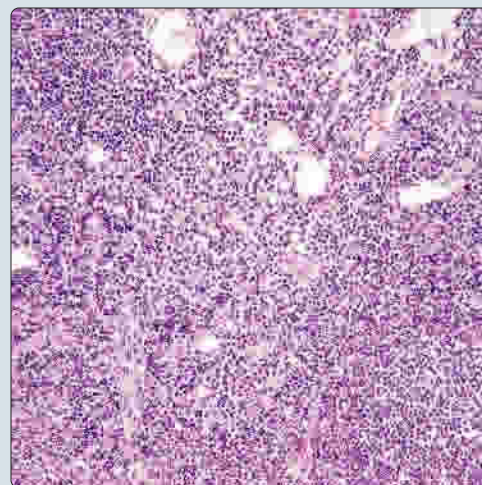


(Left) The surface epithelium is heavily spongiotic with degenerated bullae . Inflammatory cells are arranged within the surface epithelium and within the stroma below. This acute laryngitis shows predominantly acute inflammatory cells. Biopsy is seldom performed in this setting. (Right) There is a heavy inflammatory infiltrate filling the subepithelial space of this case of acute laryngitis (viral). There is a suggestion of abscess formation in this disorder.

Degenerative Bullae



Acute Viral Laryngitis



TERMINOLOGY

Synonyms

- Different terms based on specific anatomic site affected
 - Pharyngitis, laryngitis, croup, epiglottitis

Definitions

- Laryngitis can be infectious or inflammatory, acute or chronic, often multifactorial

ETIOLOGY/PATHOGENESIS

Infectious

- Many viruses, bacteria, and fungi can cause laryngitis

Trauma/Mechanical

- Foreign bodies getting caught cause ulceration, predisposing to laryngitis

Neoplasm

- Tumors can cause ulceration

Iatrogenic

- Surgery (vascular compromise), feeding or tracheostomy tube, post radiation, noxious environmental exposures (including miners)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Common (6%), with seasonal and age variability
 - Laryngitis usually clinical diagnosis
- Age
 - Same organism causes different clinical disease based on age
 - Bronchiolitis in infant; croup in older child; pharyngitis in young adult; subclinical syndrome in middle-aged adult
 - Croup: Usually < 6 years
 - Herpes: Very young, very old, pregnant, or immunocompromised patients

Presentation

- Thorough history, including occupation and vocal demands, may guide further evaluation
- Clinical manifestations depend on age, sex, nutritional and immunity status
- Croup: Hoarseness, barking cough, inspiratory stridor (noisy, labored breathing)
- Epiglottitis: Tripod sign, fever, stridor, sore throat, odynophagia, shortness of breath, drooling
- Immunocompromised patients: Herpes simplex or fungal laryngitis
 - AIDS, cancer, leukemia/lymphoma, corticosteroids, diabetes mellitus, pulmonary disease, organ transplantation
- Cord function may be compromised

Laboratory Tests

- Extensive laboratory investigation for specific infectious agent is not warranted, except in extreme or unique cases
 - Serologic pre- and postinfection titers may document infectious agent (complement fixation; precipitant tests)

Treatment

- Drugs
 - Culture sensitivities dictate type and duration of antimicrobial regimen
 - Single dose corticosteroids and bronchodilators reduce croup severity and duration
 - Nebulized epinephrine in patients with severe croup
 - Antifungal therapy if fungal organisms
- Generally, supportive measures to control symptoms

Prognosis

- Excellent for self-limited viral illnesses

MICROSCOPIC

Histologic Features

- Nonspecific inflammatory cells and edema fluid
- Surface epithelial erosion or ulceration (part of prolonged ulcerative laryngitis)
- Hyperkeratosis commonly associated with intraepithelial neutrophils
- Secondary bacterial colonies within exudate
- Pseudoepitheliomatous hyperplasia associated with fungal infections
- Multinucleated giant cells with opacified, ground-glass nuclei (herpes simplex) or prominent Cowdry A-type inclusion (CMV)
- Atrophy or hyperplasia associated with nonspecific inflammatory infiltrate in chronic laryngitis cases

ANCILLARY TESTS

Histochemistry

- Specific histochemistry stains highlight organisms: Gram, acid-fast, fluoro, GMS, PAS/light green

Immunohistochemistry

- Selectively: HSV, CMV

DIFFERENTIAL DIAGNOSIS

Gastroesophageal Reflux Disease

- Fibrinoid necrosis; granulation tissue, organized

Squamous Cell Carcinoma (SCC)

- Pseudoepitheliomatous hyperplasia in fungal infection can mimic SCC

Wegener Granulomatosis

- Biocollagenolysis; blue-granular geographic necrosis; foreign body giant cells; vasculitis, ↑ ANCA titers


Relapsing Polychondritis

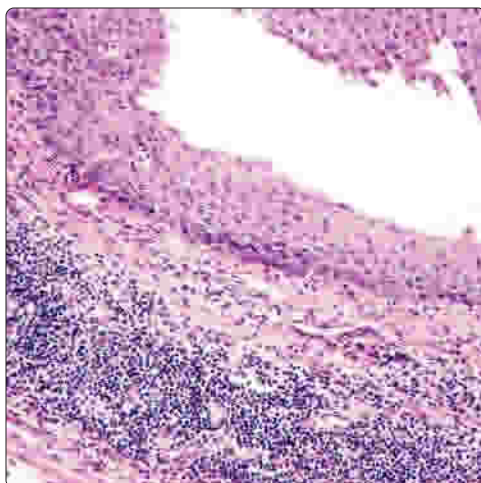
- Cartilage destroyed by mixed inflammation; no granuloma; autoantibodies

SELECTED REFERENCES

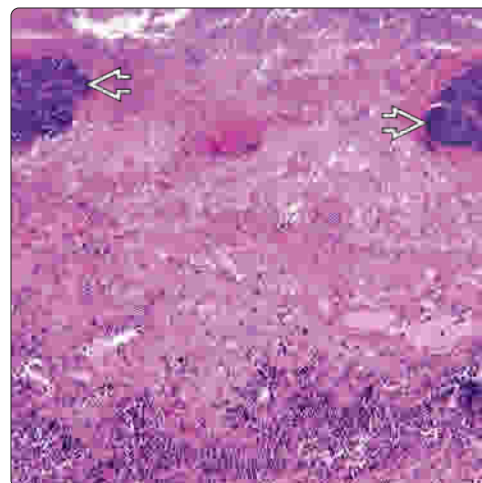
1. Witt DR et al: Detection of chronic laryngitis due to laryngopharyngeal reflux using color and texture analysis of laryngoscopic images. *J Voice*. 28(1):98-105, 2014
2. O'Neil MB et al: Ulcerative lesions as a rare cause of laryngotracheitis in the pediatric population. *Am J Otolaryngol*. 34(5):541-4, 2013
3. Tulunay OE: Laryngitis—diagnosis and management. *Otolaryngol Clin North Am*. 41(2):437-51, ix, 2008

Chronic Laryngitis



(Left) The surface epithelium is metaplastic, subtended by a band of heavy chronic inflammatory cells. This is from a case of chronic laryngitis in a patient with a long exposure to noxious fumes in the workplace. **(Right)** This case of acute viral laryngitis was associated with a secondary bacterial infection in a patient with a history of squamous cell carcinoma and radiation therapy. Bacterial colonies  are frequently seen as a concurrent finding in erosions/ulcerations.



Bacterial Colonies in Acute Laryngitis

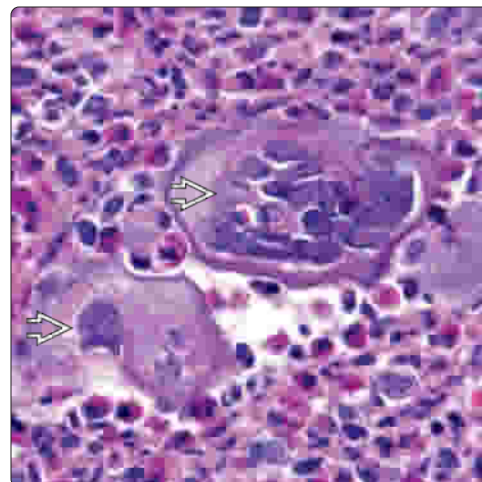


Herpes Simplex Laryngitis


(Left) There is a heavy inflammatory infiltrate composed of acute and chronic inflammatory cells. Within this background, a number of multinucleated giant cells  can be seen, part of a herpes simplex infection. This type of giant cell is pathognomonic for herpes infections. **(Right)** The characteristic multinucleated giant cells of herpes simplex infection  are shown. Note the nuclear overlapping and the powdery, smudged nuclear chromatin within the giant cells.

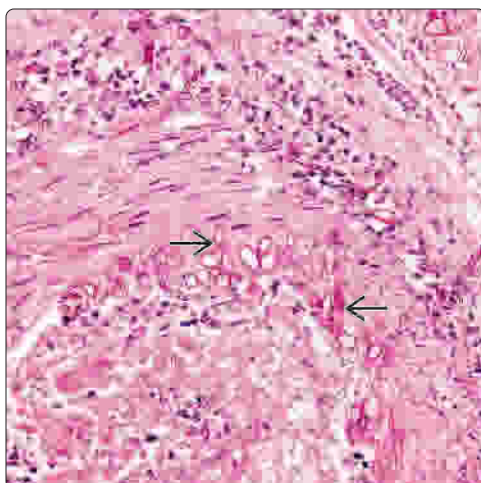


Multinucleated Giant Cells of Herpes Simplex

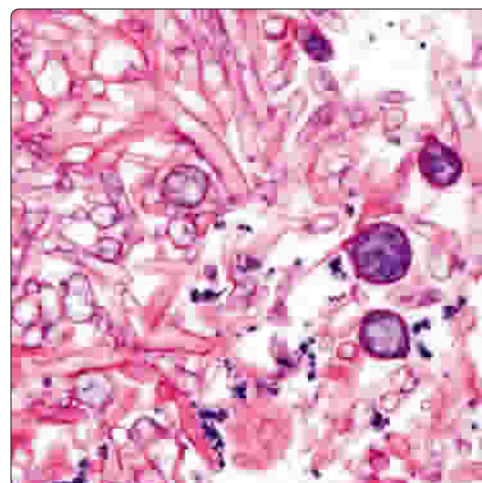


Vessel Invasion by Fungal Hyphae

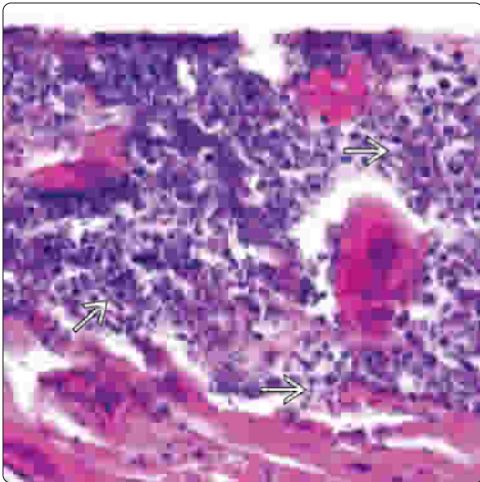
(Left) Fungal infections can involve the surface epithelium or present as deep fungal infections. This deep fungal infection shows numerous fungal hyphae within a vessel wall . **(Right)** There are fungal hyphae and spores of mucormycosis within the larynx biopsy of a patient with systemic infection. Aggressive antifungal therapy is required for this type of "invasive" laryngitis.



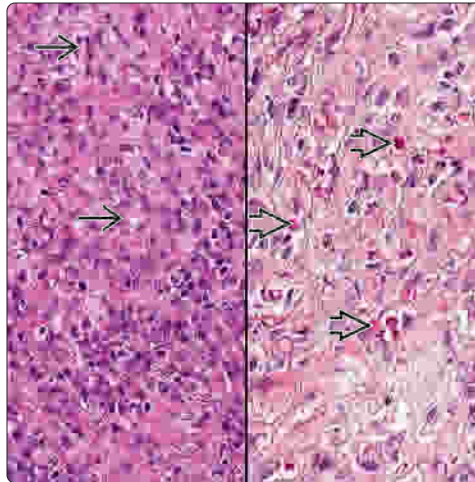
Mucormycosis in Laryngitis



Candida Species in Candida Laryngitis

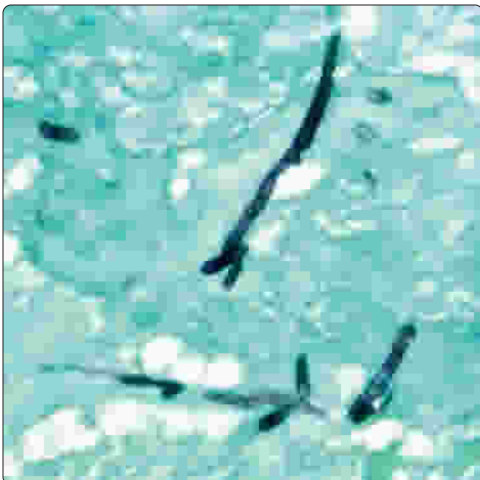


Cryptococcal Laryngitis



(Left) The keratin is filled with fungal spores, although well-developed fungal hyphae are noted throughout. It is required to see fungal hyphae attached to the keratin to qualify as a legitimate fungal infection. (Right) The tissue shows a heavy granulomatous-type inflammation. Cleared spaces can be seen but organisms are not easily identified. However, with a mucicarmine stain, the cryptococcal organisms are highlighted in magenta, present throughout the sample.

Fungal Hyphae Identified by GMS

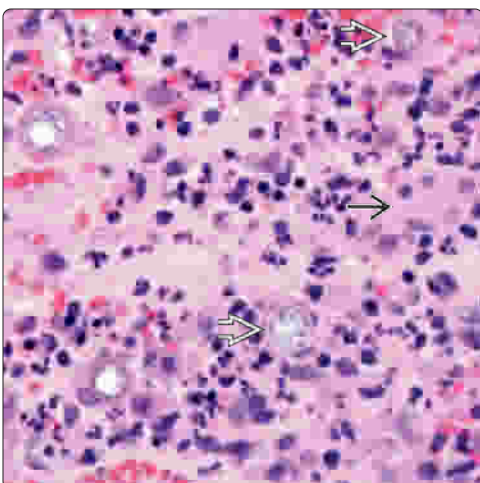


Trichinella in Muscles of Larynx

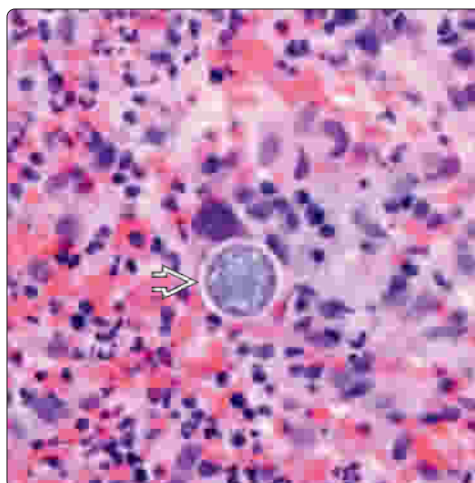


(Left) A silver impregnation stain highlights numerous fungal hyphae in this example of fungal laryngitis. This type of finding requires antifungal chemotherapy agents (amphotericin B or azoles). (Right) Parasitic infections are quite uncommon in the larynx; however, trichinellosis can be seen in patients with systemic disease.

Coccidiomycosis Spherules



Coccidiomycosis Spherule in Laryngitis



(Left) Coccidiomycosis infection of the larynx is shown with numerous spherules filled with endospores. There is a mixed inflammatory infiltrate & background giant cell formation. (Right) Coccidiomycosis infection of the larynx can be seen as part of systemic disease. The spherule filled with endospores is characteristic for this type of fungal organism. Note the mixed inflammatory infiltrate & background giant cell formation.

Vocal Cord Nodules and Polyps

KEY FACTS

TERMINOLOGY

- Reactive changes of laryngeal mucosa and adjacent stroma, which results in benign polypoid or nodular growth
- However, clinicopathologic separation between nodules, polyps, and Reinke edema is neither clinically reproducible nor histologically unique

ETIOLOGY/PATHOGENESIS

- Laryngeal trauma may result from vocal abuse, accidents, or surgery
- Hypothyroidism

CLINICAL ISSUES

- Excessive and improper use of voice
- Patients present with hoarseness and phonation changes
- Nodule: Nearly always bilateral < 0.3 cm nodule on anterior to middle 1/3 of vocal cord
- Polyp: > 90% unilateral, ventricular or Reinke space, > 0.3 cm raspberry-like mass

- Voice therapy is first-line treatment
 - Surgery for refractory cases

MICROSCOPIC

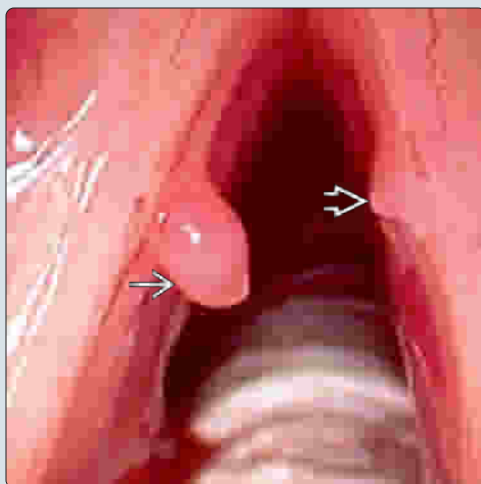
- Shows arc of development (histologic features based on phase at time of biopsy)
- Edema, proteinaceous subepithelial deposition
- Loose myxoid matrix associated with hemorrhage and vascularized stroma
- Dilated vessels (telangiectasia) associated with granulation tissue and hemorrhage/fibrin
- Myxoid, pale blue-pink material
- Fibrous connective tissue deposition

TOP DIFFERENTIAL DIAGNOSES

- Amyloidosis, contact ulcer, ligenous conjunctivitis
- Myxoma, spindle cell squamous cell carcinoma, granular cell tumor

Laryngoscopic Appearance

(Left) A polypoid projection from the vocal cord ➡ is noted. There is a slight nodularity on the contralateral vocal cord ➡, suggesting "bilateral" disease. Contact ulcer is more commonly bilateral, but affects the posterior cords. **(Right)** The overlying squamous mucosa is intact. There is an edematous stroma with fibrinous degeneration of the stroma. Hyaline deposition is noted. Inflammatory cells are present, but are sparse in this early stage polyp.



Edematous Polyp

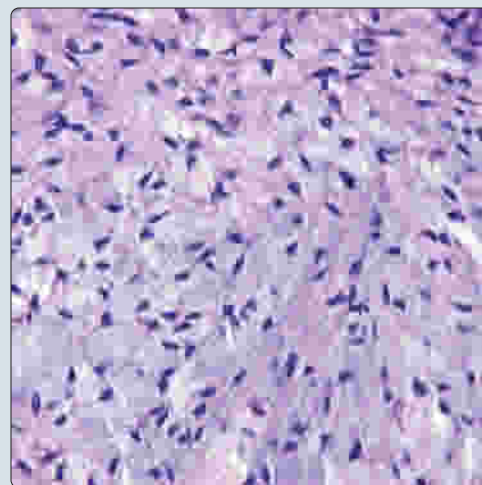


Fibrinous Polyp

(Left) An intact surface epithelium is usually seen in most polyps. However, the stroma is filled with blood and with fibrin deposition ➡. The fibrin may sometimes mimic amyloid deposition. **(Right)** High-power H&E image shows only the myxoid stroma deep within the polyp. The stroma can be quite cellular, as shown in this example, while in other cases there may be a very sparse cellularity. The myxoid material is usually bluish to pale, identified between the fibroblasts.



Myxoid Change in Polyp



TERMINOLOGY

Synonyms

- Nodule
- Polyp

Definitions

- Reactive changes of laryngeal mucosa and adjacent stroma, which results in benign polypoid or nodular growth
- However, the clinicopathologic separation between nodules, polyps, and Reinke edema is neither clinically reproducible nor histologically unique

ETIOLOGY/PATHOGENESIS

Multifactorial

- Laryngeal trauma may result from vocal abuse, accidents, or surgery
 - Excessive and improper use of voice
 - Iatrogenic or functional lesions
- Infection
- Hypothyroidism
- Smoking

Pathogenesis

- Personality traits, specifically extroversion, associated with development of vocal cord polyps and nodules

CLINICAL ISSUES

Epidemiology

- Incidence
 - Infrequent
 - ~ 1.5% of population has hoarseness
 - Polyp/nodule is one of the most frequent significant causes of hoarseness
 - ~ 2.5% of children have nodules (prevalence)
- Age
 - Variable between nodule or polyp
 - Nodule
 - Usually young to middle-aged patients
 - Uncommon in children
 - Polyp: Any age group
- Sex
 - Nodule
 - Female > male in young patients
 - Boys > girls (~ 2:1) in children (7-16 years old)
 - Polyp: Equal gender distribution

Site

- Nodule
 - Anterior to middle 3rd of true vocal cord
 - Nearly always bilateral
- Polyp
 - Aryepiglottic fold, ventricular space, vocal fold, Reinke space
 - > 90% unilateral

Presentation

- Behavior-induced vocal changes
 - Affects speaking voice of nonprofessionals and professionals

- Professional voice users
- Singers, actors, public speakers, lecturers, coaches
- Excessive (overuse) and improper (abuse) use of voice
- Stressing or straining of voice
- Disease-related vocal cord disease
 - Infection
 - Hypothyroidism
 - Smoking association
- Hoarseness
- Phonation changes

Endoscopic Findings

- Laryngoscopic and stroboscopic findings can be combined in reaching diagnosis
- Nodules more frequently bilateral, sometimes showing hemorrhage
- Polyps appear as protuberances, erythematous, and edematous
- Digital kymography provides objective quantitative data about vocal fold vibration
 - Amplitude symmetry and vocal cord location can aid in separation between nodule and polyp
- Use of ultrasonography and virtual laryngoscopy may be of benefit
 - Spectrophotometric analysis of hemoglobin concentration in various disease conditions may help clinical assessment
 - Lower hemoglobin concentrations in polyps

Treatment

- Options, risks, complications
 - Among professional voice users, voice problems have significant personal negative impact
 - Ability to work, overall sense of well-being, sense of self
- Surgical approaches
 - Little evidence for surgical intervention as first-line therapy
 - If needed, either CO₂ laser &/or microdissection are equivalent modalities
- Management strategies include voice reeducation, drug therapy, and surgery
- Voice therapy is first-line treatment
 - Good vocal function is required by more than 1/3 of labor force to fulfill their job requirements
 - Behavior modification
 - General vocal hygiene is beneficial
 - If there is no improvement with initial speech and language therapy, referral to specialist voice clinic (speech pathologist) should be considered
- Treatment of hypothyroidism can be beneficial

Prognosis

- Excellent, usually without any long-term follow-up required
- Recurrences if inciting factor is not identified and removed or managed

MACROSCOPIC

General Features

- Nodule
 - Bilateral, affecting opposing surfaces of vocal cords

- o Usually middle to anterior 1/3 of vocal cord
- o Range from edematous, gelatinous, hemorrhagic, firm or fixed
- Polyp
 - o Single
 - o Soft, rubbery mass
 - o Translucent to red
 - o Sessile
 - o Raspberry-like to pedunculated

Size

- Nodule: Usually < 0.3 cm
- Polyp: Usually > 0.3 cm
 - o Can be up to a few centimeters

MICROSCOPIC

Histologic Features

- No definitive histological distinction between laryngeal nodules and polyps
- Arc of development
 - o Edema and proteinaceous material deposited in interstitium and subepithelial tissue
 - o Loose myxoid matrix associated with hemorrhage within vascularized stroma
 - Inflammation is usually sparse to absent
 - o Dilated vessels (telangiectasia) associated with granulation tissue and hemorrhage/fibrin
 - o Myxoid, pale blue-pink material may predominate
 - o Fibrous connective tissue deposition
 - Fibrin-type material adjacent to vascular spaces
 - May become completely collagenized/fibrotic at end stage
 - Thickened basement membrane in nodules >>> polyps
 - Only isolated fibroblasts present
- Polyps divided into 4 main histologic subtypes depending on stage of development at time of biopsy and dominant histologic pattern
 - o Edematous
 - o Vascular
 - o Myxoid
 - o Hyaline or fibrous
 - Not uncommon to have overlap or mixture of these features
- Surface epithelium
 - o Metaplastic, atrophic (nodule), keratotic, or hyperplastic (polyp), but not usually atypical or pleomorphic
- Crystals rarely identified in some polyps

DIFFERENTIAL DIAGNOSIS

Amlyoidosis

- False vocal cord most common
- Acellular, extracellular, eosinophilic, matrix material
- Perivascular and periglandular accentuation
- **Positive** with Congo red &/or cresyl violet
- Uncommonly, may show light chain restriction (κ or λ)

Myxoma

- Uncommon mass lesion
- Hypocellular myxoid lesion with stellate spindle cells

- Usually clear to very light blue matrix
- Difficult to separate from myxoid polyp in some cases

Spindle Cell Squamous Cell Carcinoma

- Polypoid mass with surface ulceration or denudation
- Epithelium can be identified (usually in crypts or base of polyp)
- Cellular stroma, comprised of atypical spindled cells with pleomorphism and nuclear hyperchromasia
- Mitotic figures increased, including atypical forms
- May be **positive** with keratin (~ 70% of cases) immunohistochemistry
- Proliferation markers tend to be increased

Contact Ulcer

- Bilateral, polypoid mass on opposing surfaces of posterior true vocal cords
- Surface ulceration with fibrinoid necrosis
- Granulation tissue with vessels arranged perpendicular to surface
- Inflammation with hemosiderin-laden macrophages
- Mitotic figures can be seen (vessels or fibroblasts)

Granular Cell Tumor

- Pseudoepitheliomatous hyperplasia of epithelium
 - o Directly overlying neoplastic cells only
- Large polygonal cells with abundant, granular, eosinophilic cytoplasm
- Frequently associated with nerves
- Strong S100 protein and CD68 immunoreactivity

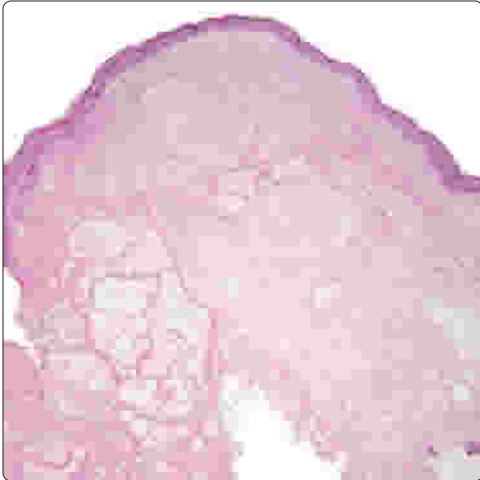
Ligneous Conjunctivitis

- Uncommon in larynx
- Hard, subepithelial nodule
- Firm, clotted fibrin-rich matrix material deposition

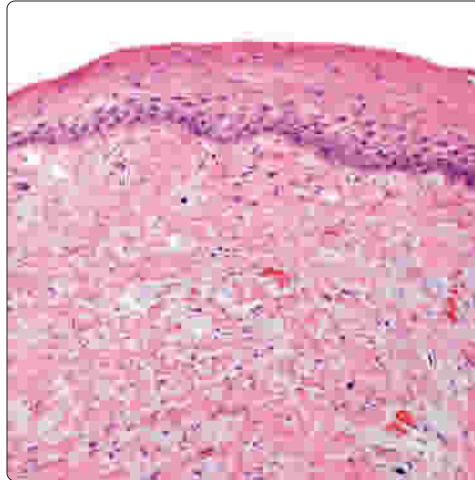
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Laryngeal Polyp

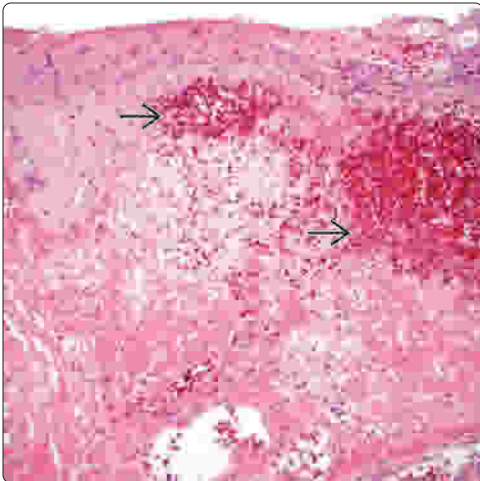


Early Fibrous Deposition in Polyp

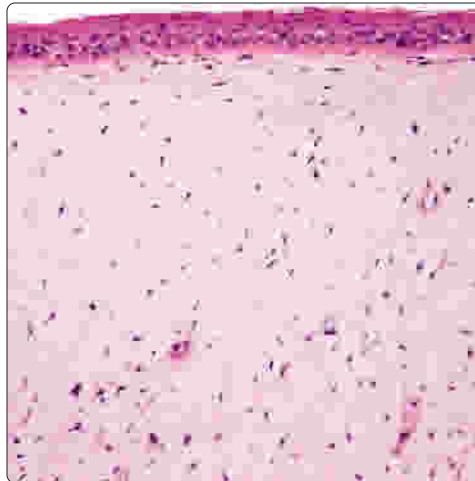


(Left) Low-power view shows the overall polypoid shape of the specimen. There is an intact surface squamous epithelium. Note the numerous vascular channels and degenerative-type changes associated with the edema in the stroma. **(Right)** There is a mixed fibrous connective tissue stroma with myxoid material between the fibrosis. This is a common finding in the arc of development seen in a polyp/nodule.

Hemorrhagic Polyp

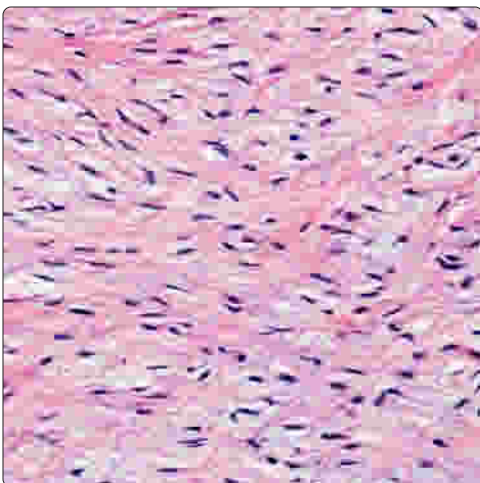


Myxoid Change in Laryngeal Polyp



(Left) Early in the development of a polyp, there is edema and hemorrhage into the stroma below an intact or possibly ulcerated epithelium. Fibrinous material is noted in the stroma as organization of the hemorrhage is suggested. **(Right)** The stroma is hypocellular in this polyp, although there is a very edematous to myxomatous stroma. There are a few isolated spindle cells in the stroma, but they are not atypical. Mitotic figures are absent.

Myxoid-Fibrous Polyp



Fibrous Polyp (Nodule)



(Left) As the arc of development for a polyp continues, there is a mingling of myxoid matrix with the fibrous connective tissue stroma. Note the bland spindle fibroblastic cells. **(Right)** The end stage of a polyp/nodule shows heavy subepithelial fibrosis, sometimes creating an accentuated basement membrane material. The epithelium may be hyperplastic, with keratosis. However, cellular atypia is absent in this case. It is important to know that dysplasia or carcinoma may be seen concurrent with a polyp.

Reactive Epithelial Changes

KEY FACTS

TERMINOLOGY

- **Keratosis:** Keratin layer on surface of squamous epithelium, often accompanied by granular cell layer
- **Pseudoepitheliomatous hyperplasia (PEH):** Extensive hyperplasia of squamous epithelium without cytologic atypia, with irregular projections into stroma
- **Radiation change (RC):** Affects surface epithelium, minor salivary glands, fibrous tissue, vessels, and cartilages

CLINICAL ISSUES

- Hoarseness, cough, foreign body sensation, airway obstruction, dysphagia
- Raised, flat, or sometimes ulcerated
- Leukoplakia or erythroplakia

MACROSCOPIC

- Keratosis: Usually well-circumscribed, slightly elevated white plaque of vocal cord

- PEH: Thickening or polypoid lesion with smooth, whitish surface
- RCs: Early (edema, mucositis, ulceration, blood) vs. late (atrophic or hyperplastic mucosa, fibrosis, glottic stenosis, osteonecrosis)

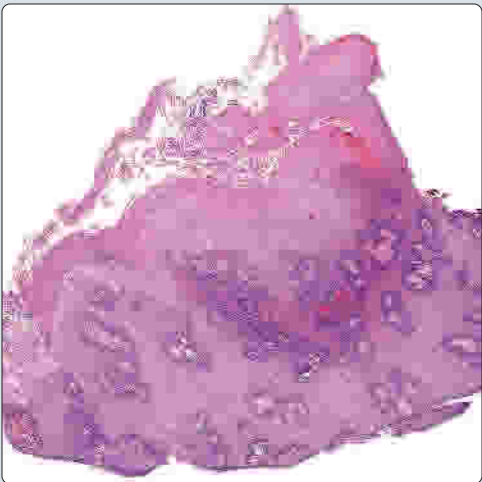
MICROSCOPIC

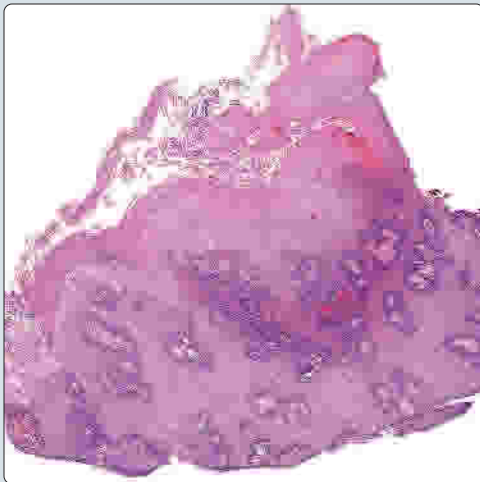
- Keratosis is variably thickened keratotic layer \pm nuclei; granular layer may be present; irregularly hyperplastic spinous layer; possible chronic inflammation
- PEH shows hyperplastic epithelium without atypia, well-defined basement membrane with irregular epithelial projections into stroma
- RCs have stages: Ductal squamous metaplasia, endothelial cell hypertrophy, bizarre fibroblasts in dense fibrosis, bizarre skeletal muscle changes

TOP DIFFERENTIAL DIAGNOSES

- Invasive squamous cell carcinoma, dysplasia, gouty tophus

Keratosis With Hyperplasia

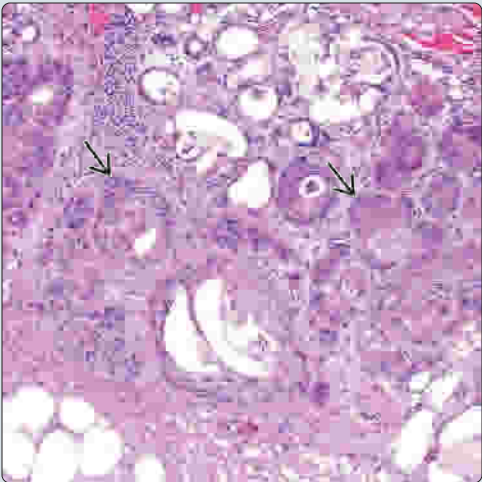

(Left) Keratosis is shown with a keratin layer on surface of a hyperplastic squamous epithelium, often accompanied by a granular cell layer. There may be verrucous hyperplasia concurrently. **(Right)** Hematoxylin and eosin shows irregular epithelial projections of pseudoepitheliomatous hyperplasia (PEH) expanding into underlying stroma. Note the well-formed nests with a defined basement membrane. There is a granular cell tumor in the stroma .

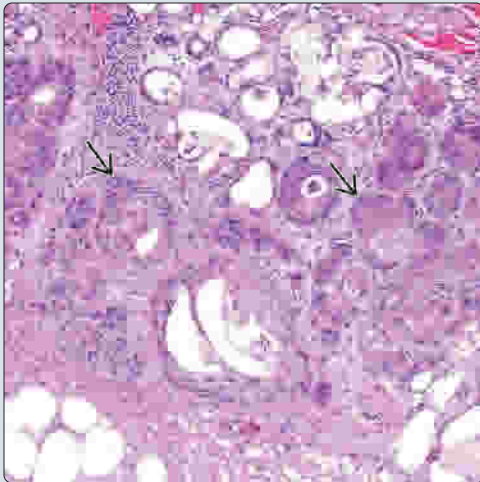


Pseudoepitheliomatous Hyperplasia



Necrotizing Sialometaplasia

(Left) There is squamous metaplasia of the minor mucoserous glands  that are noted in the background, maintaining a lobular architecture with a well-defined basement membrane. **(Right)** Hematoxylin and eosin shows Teflon particles surrounded by multinucleated giant cells . Teflon particles of oval and rounded shape have clear centers and darker borders. Teflon is rarely used today.



Teflon Granuloma



TERMINOLOGY

Synonyms

- Leukoplakia
- Keratosis without atypia
- Pseudoepitheliomatous hyperplasia (PEH)

Definitions

- Keratosis
 - Keratin layer on surface of squamous epithelium, often accompanied by granular cell layer
- PEH
 - Extensive hyperplasia of prickle cell layer of squamous epithelium without cytologic atypia
 - Has irregular epithelial projections into underlying stroma mimicking squamous cell carcinoma
- Radiation change (RC)
 - Long-lasting or life persistent morphologic changes caused by radiotherapy
 - Affects surface epithelium, minor salivary glands, fibrous tissue, vessels, and cartilages

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Keratosis: Smoking, air pollution, chronic irritation
- PEH: Chronic irritation, smoking
- RC: Radiation therapy of larynx, usually for carcinoma, but may be part of head and neck radiation for different reason
- Teflon granuloma (TG): Injection of Teflon paste (tetrafluoroethylene and glycerin)

Infectious Agents

- Various bacteria and fungi can cause PEH
 - Mycobacteria, *Blastomyces dermatitidis*, *Cryptococcus*

Tumor

- Granular cell tumor is frequently associated with PEH

CLINICAL ISSUES

Site

- Specific anatomic site for certain types of reactive changes
 - True vocal folds/cords: Keratosis, PEH, and TG
 - Posterior true vocal folds, false cords, and subglottis: Granular cell tumor and PEH
 - Any site for radiation

Presentation

- Hoarseness, cough, foreign body sensation, airway obstruction, dysphagia

Endoscopic Findings

- Raised, flat, or sometimes ulcerated
- Leukoplakia or erythroplakia
- Findings are usually nonspecific and can significantly overlap with carcinoma

Natural History

- Most reactive conditions resolve spontaneously, if etiologic agent is removed

Treatment

- Most lesions resolve on their own

- Endoscopic removal provides diagnosis, rather than treatment

Prognosis

- No risk of malignant transformation if atypia or dysplasia is absent

MACROSCOPIC

General Features

- Keratosis: Usually well-circumscribed, slightly elevated white plaque of vocal cord
- PEH: Thickening or polypoid lesion with smooth, whitish surface
- RCs
 - Early: Edema, mucositis, ulceration, blood
 - Late: Atrophic or hyperplastic mucosa, fibrosis, glottic stenosis, osteonecrosis

MICROSCOPIC

Histologic Features

- Keratosis is variably thickened keratotic layer \pm nuclei; granular layer may be present; irregularly hyperplastic spinous layer; possible chronic inflammation
- PEH shows hyperplastic epithelium without atypia, well-defined basement membrane with irregular epithelial projections into stroma
 - Exclude granular cell tumor; special studies to exclude infectious agent
- RCs have stages
 - Acute stage: Acute necrotizing inflammation
 - Chronic stage: Surface ulceration, squamous atypia, atrophic epithelium, and minor salivary glands
 - Ductal squamous metaplasia, endothelial cell hypertrophy, bizarre fibroblasts in dense fibrosis, bizarre skeletal muscle changes
 - Rarely, chondronecrosis or osteonecrosis

DIFFERENTIAL DIAGNOSIS

Squamous Cell Carcinoma

- PEH can mimic invasive carcinoma
- Invasive growth of pleomorphic epithelial cells, increased mitoses, including atypical forms

Dysplasia or Carcinoma

- Radiation change or PEH may result in overestimation of grade of dysplasia or invasive SCC

Gouty Tophus (for TG)

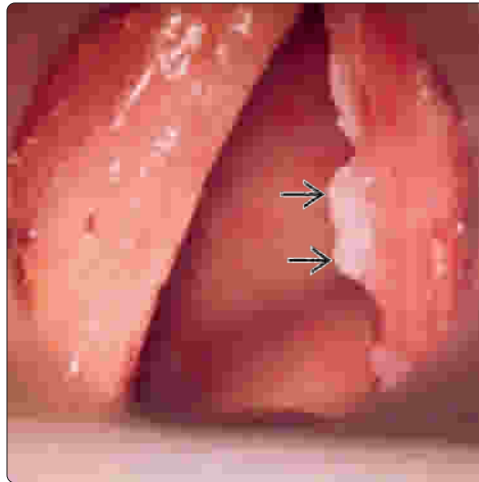
- Amorphous crystals, enveloped by giant cells and histiocytes
- Needle-shaped crystals on unstained sections

SELECTED REFERENCES

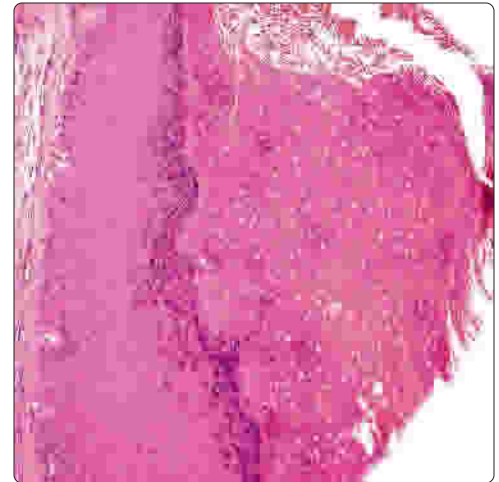
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Leukoplakia of Vocal Cord

(Left) Endoscopic view shows a well-circumscribed, uneven, exophytic white plaque (leukoplakia) on the right vocal cord. This clinical appearance encompasses a wide variety of histologic changes. **(Right)** Hematoxylin and eosin shows hyperplastic squamous epithelium with a keratohyaline layer and an exuberant layer of keratin (termed keratosis). Parakeratosis is not appreciated, but orthokeratosis is. There is no cytologic atypia.



Keratosis With Orthokeratosis

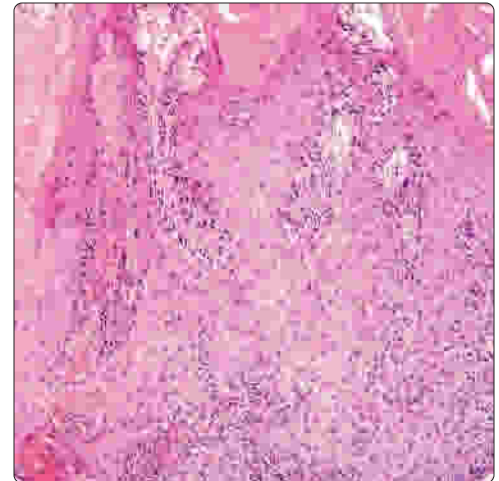


Verrucous Hyperplasia

(Left) Verrucous hyperplasia is an extreme version of keratosis. In this case, there is a well-defined base with keratosis and parakeratosis. **(Right)** Verrucous hyperplasia is difficult to diagnose accurately. There is abundant keratin, projections of epithelium, and a lack of cytologic atypia. However, verrucous squamous cell carcinoma can have these same features, especially if the biopsy is superficial.

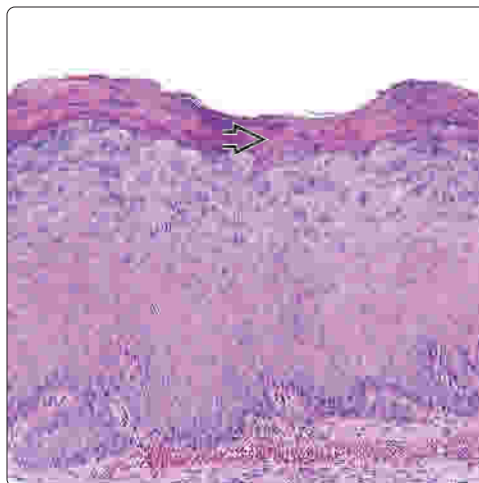


Verrucous Hyperplasia With Keratosis

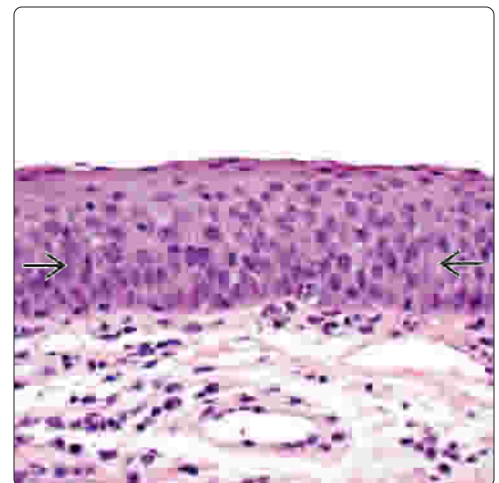


Hyperplasia With Keratosis

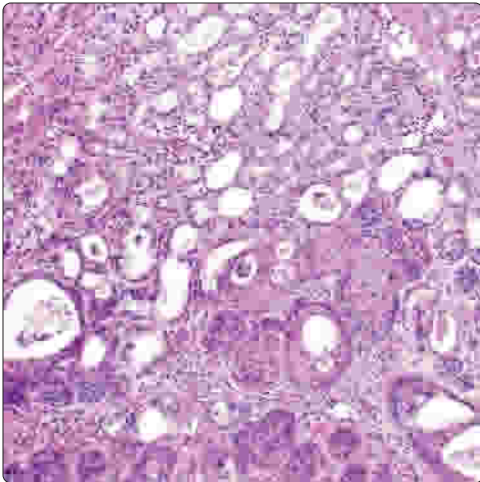
(Left) The squamous epithelium is thickened, showing a prominent granular cell layer and keratosis. There is associated parakeratosis in this case, too. **(Right)** The basal zone of the epithelium is thickened in this example of basal cell hyperplasia. Basal hyperplasia is quite frequently identified at the transition from one epithelium to another and should not be confused for dysplasia. There is a lack of atypia.



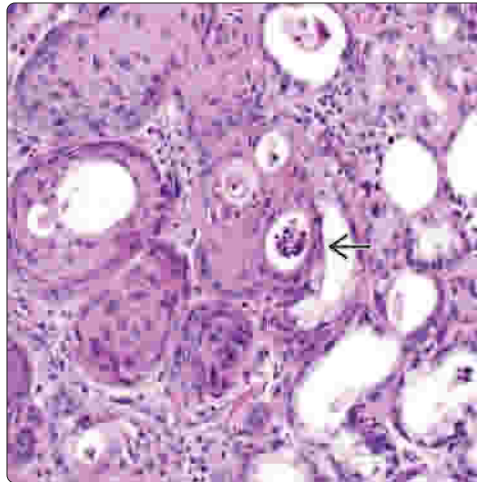
Basal Zone Hyperplasia




Low Power of Necrotizing Sialometaplasia

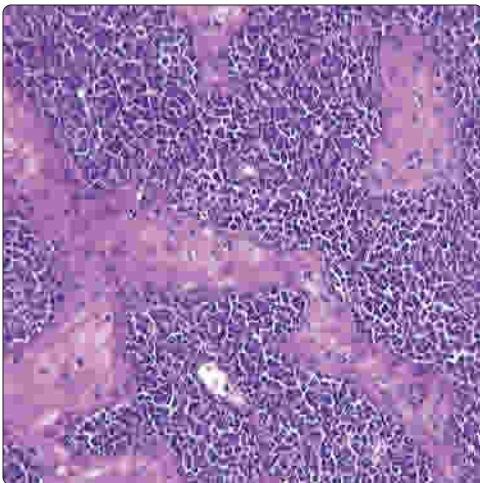


High Power of Necrotizing Sialometaplasia

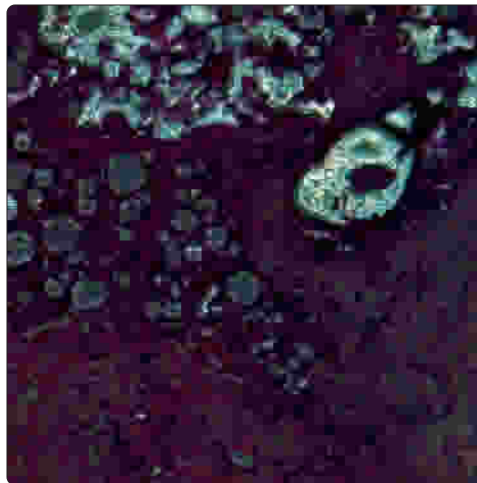


(Left) The lower portion of the field highlights the sialometaplasia by squamous epithelium, while the upper field shows numerous minor mucoserous glands. The lobular appearance of the proliferation is easily identified. (Right) A minor mucoserous gland shows early squamous metaplasia , 1 of the findings in sialometaplasia. The lobular outline of the glands/ducts is still maintained, even though there may be some cellular atypia.

Pseudoepitheliomatous Hyperplasia

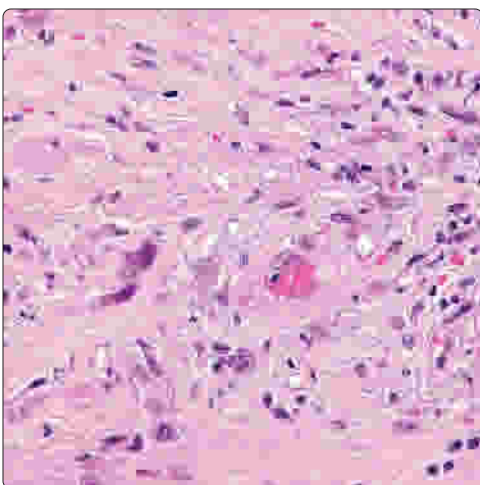


Teflon Material Under Polarized Light

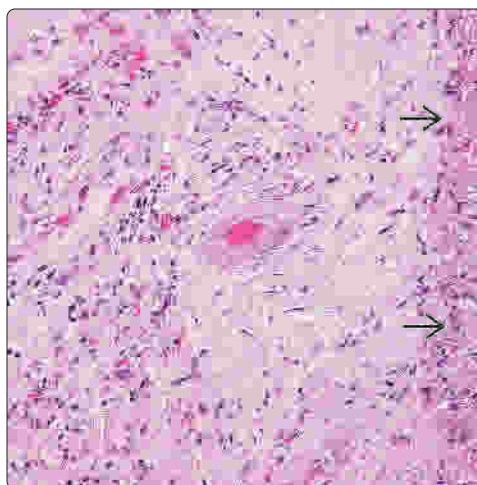




(Left) This area of PEH shows a squamous epithelium with a well-defined border set within a very heavily inflamed stroma. This is an uncommon finding. (Right) The Teflon particles appear quite prominent and polarizable under polarized light. Talc may polarize but would appear differently on H&E stained material. The crystals of gout are sheaf-like and are not arranged in this fashion.

Radiation Changes With Nuclear Atypia



Radiation Changes and Surface Necrosis



(Left) Hematoxylin and eosin shows radiation-induced changes as fibrosis, mixed cell-type inflammatory reaction, and pleomorphic-appearing fibroblasts with hyperchromatic atypical nuclei. However, the nuclear:cytoplasmic ratio is maintained. (Right) Hematoxylin and eosin shows radiation-induced changes of laryngeal mucosa with surface necrosis , increased fibrosis, and mixed cell-type inflammatory infiltration. .

Contact Ulcer

KEY FACTS

TERMINOLOGY

- Benign reactive epithelial response to injury

ETIOLOGY/PATHOGENESIS

- Gastroesophageal reflux disease (GERD)
 - Especially when recumbent, gastric fluids reflux past posterior vocal cords, resulting in acid denudation of the mucosa

CLINICAL ISSUES

- Male > female (except postintubation)
- Posterior larynx (true vocal cord, posterior commissure)
- Hoarseness, cough, sore throat, vocal abuse/misuse, chronic throat clearing
- Heartburn as part of gastroesophageal reflux disease (gastrolaryngeal reflux)
- Remove inciting factor or surgery

MACROSCOPIC



- Bilateral, polypoid masses, resulting in kissing ulcer on contralateral cord

MICROSCOPIC

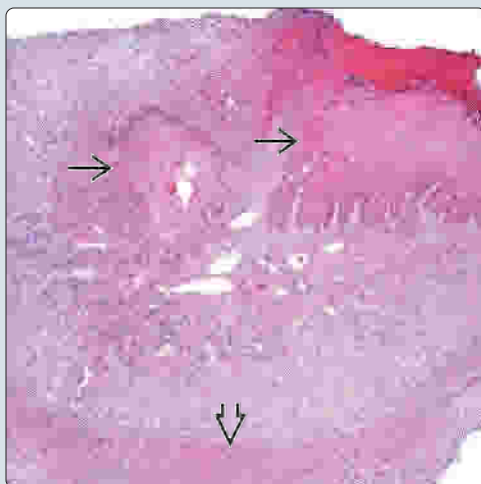
- Surface ulceration
- Significant fibrinoid necrosis at surface
- Exuberant granulation tissue
- Hemosiderin-laden macrophages (especially at base)
- Surface regeneration or reepithelialization with time
 - Fibrinoid necrosis is still present immediately below surface (clue to diagnosis)

TOP DIFFERENTIAL DIAGNOSES

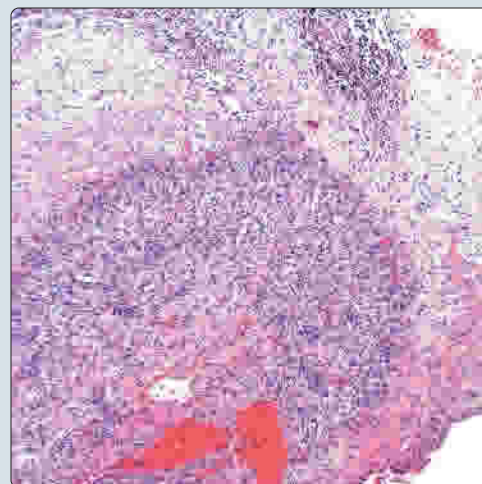
- Pseudoepitheliomatous hyperplasia
- Squamous cell carcinoma, including spindle cell type
- Vascular tumors
- Inflammatory conditions

(Left) The surface epithelium  has been nearly completely denuded , with marked fibrinoid necrosis covering the polyp in this contact ulcer. A rich granulation tissue is noted. **(Right)** The polyp shows a central core of granulation tissue covered by a fibrinoid necrosis and lack of any surface epithelium (completely denuded). It is not uncommon for a contact ulcer to lose all epithelium.

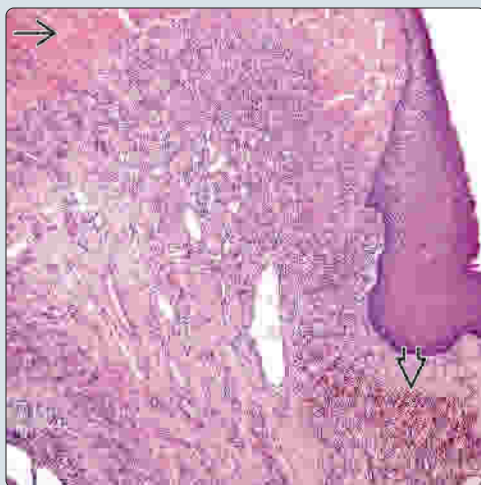
Polypoid Mass With Surface Ulceration






Denuded Polyp With Granulation Tissue



Granulation Tissue With Hemosiderin Laden Macrophages



(Left) Hematoxylin and eosin shows fibrinoid necrosis , ulceration, and perpendicular vessels with granulation tissue and hemosiderin-laden macrophages . Note that the squamous epithelium is beginning to reepithelialize the surface. **(Right)** The surface epithelium has nearly completely grown over the area of previous ulceration in this contact ulcer. Several islands of entrapped epithelium  are seen within the persistent fibrinoid necrosis.

Entrapped Epithelium in Fibrinoid Necrosis



TERMINOLOGY

Synonyms

- Pyogenic, intubation or vocal process granuloma
- Peptic granuloma

Definitions

- Benign reactive epithelial response to injury

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Gastroesophageal reflux disease (GERD)
 - Gastric fluids reflux against posterior vocal cords, resulting in chemical denudation of mucosa
- Intubation complication, especially when incorrect endotracheal tube is used emergently
 - More common in females than males
- Vocal abuse

CLINICAL ISSUES

Epidemiology

- Incidence
 - Frequent
 - Increased incidence in GERD
- Age
 - Usually adults
- Sex
 - Male > female (except postintubation)

Site

- Posterior larynx (true vocal cord, posterior commissure)

Presentation

- Hoarseness, cough, sore throat, vocal abuse/misuse, chronic throat clearing
- Heartburn as part of gastroesophageal reflux disease (gastroesophageal reflux)

Treatment

- Remove inciting factor
 - Aggressive acid-suppressive therapy to control GERD
 - Discontinue habitual coughing, throat clearing, shouting
 - Vocal rehabilitation (especially in singers)
- Excision, usually of bilateral lesions

Prognosis

- Excellent

MACROSCOPIC

General Features

- Bilateral, polypoid masses affecting posterior larynx (kissing ulcer on contralateral cord)

Size

- Up to 3 cm

MICROSCOPIC

Histologic Features

- Surface ulceration
- Significant fibrinoid necrosis at surface

- Exuberant granulation tissue
- Vessels in granulation tissue are often perpendicular to surface
- Endothelial cells are plump and reactive but not atypical
- Rich investment with lymphocytes, plasma cells, neutrophils, and histiocytes
- Hemosiderin-laden macrophages (especially at base)
 - Increased in frequency with prolonged clinical history
- Surface bacterial overgrowth can be seen
- Surface regeneration or reepithelialization with time
 - Fibrinoid necrosis is still present immediately below surface (clue to diagnosis)
 - Epithelial hyperplasia with reactive atypia
 - Entrapped islands of epithelium can mimic invasive squamous cell carcinoma (SCC)
 - Prominent fibrosis in stroma with time

DIFFERENTIAL DIAGNOSIS

Pseudoepitheliomatous Hyperplasia

- Primarily epithelial response with thickened epithelium, rounded rete and concurrent ortho- and parakeratosis
- Fibrinoid necrosis and granulation tissue usually absent

Squamous Cell Carcinoma

- Superficially invasive SCC shows individual cell or small islands of invasion, cellular pleomorphism, desmoplastic stroma, and atypical mitoses
- Lacks fibrinoid necrosis

Spindle Cell Sarcomatoid Squamous Cell Carcinoma

- Atypical spindle cell population, limited vascularity with increased mitotic figures, including atypical forms

Vascular Tumors

- Very rare, but angiosarcoma or Kaposi sarcoma may occur
 - Show significant pleomorphism, freely anastomosing vessels, atypical mitotic figures, and hyaline, eosinophilic globules (in Kaposi)

Inflammatory Conditions

- Wegener granulomatosis: Geographic, biocollagenolytic, blue granular necrosis, vasculitis, and rare granulomas
- Special stains can be used to exclude infectious agent

DIAGNOSTIC CHECKLIST

Important Pearls

- Nearly always involves posterior larynx
- Subepithelial fibrinoid necrosis with entrapped epithelium is characteristic of surface reepithelialization

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Squamous Papilloma

KEY FACTS

ETIOLOGY/PATHOGENESIS

- Multiple benign papillary tumors related to HPV infection
 - Genotypes 6 or 11 most often
- HPV in basal cells of squamous epithelium through microtraumatized spots

CLINICAL ISSUES

- 4.3 per 100,000 people (USA Data), with increased incidence in lower socioeconomic level
- Endolarynx, rarely spread to trachea, bronchi, hypopharynx, and oropharynx
- Presentation varies based on age
 - Children: Usually before 5 years
 - Adults: Usually between 20 to 40 years
- Male > Female (3:2) in adults
- Treated with multiple surgeries with microdebrider (suction affected tissue)
 - CO₂ laser can be used
- Can be treated with antiviral drugs

MACROSCOPIC

- Usually involves true and false vocal cords
- Subglottis and ventricles involved less frequently

MICROSCOPIC

- Papillary branching projections of squamous epithelium overlying fibrovascular stroma
- Basal-parabasal cell hyperplasia
- Koilocytes in upper part of epithelium
- Atypical epithelium rarely appeared


ANCILLARY TESTS

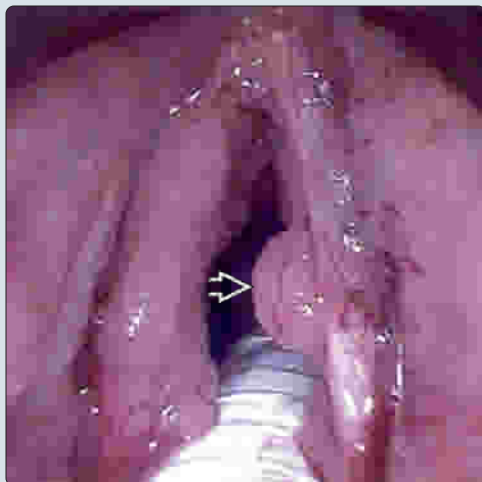
- HPV detection: Immunohistochemistry, ISH, PCR

TOP DIFFERENTIAL DIAGNOSES

- Adult solitary keratinizing squamous papilloma
- Verrucous carcinoma
- Papillary squamous cell carcinoma

Endoscopic View of Squamous Papilloma


(Left) Laryngoscopy shows a single papilloma  projecting into the laryngeal lumen. Sometimes a more filiform or papillary architecture can be seen clinically. (Right) Gross photograph shows a sessile growth with a finely lobulated surface. This pattern matches the histologic features of multiple bulbous projections of epithelium. There is no ulceration.



Gross Image of Squamous Papilloma



Multiple Projections in Squamous Papilloma

(Left) There are multiple projections of squamous epithelium surrounding delicate fibrovascular cores. The complexity of papillary structures is often due to tangential sectioning. (Right) The papillary frond is sectioned tangentially (perpendicular to the fibrovascular core). There are many koilocytes  identified at the surface, the most common location to document their presence.



Koilocytic Atypia



TERMINOLOGY

Abbreviations

- Squamous papilloma (SP)

Synonyms

- Recurrent respiratory papillomatosis

Definitions

- Benign epithelial tumor arranged in exophytic fashion of branching fronds, showing fibrovascular tissue covered by squamous epithelium, causally related to human papillomavirus (HPV) infection

ETIOLOGY/PATHOGENESIS

Infectious Agents

- HPV infection
 - Genotypes 6 or 11
 - Rarely genotypes 16, 18, 31, 33, 35, 39 of > 100 types
- Different modes of infection based on age at presentation
 - Children
 - Perinatal transmission from infected mother to child
 - Adults
 - Sexual transmission, reactivation of perinatally acquired infection

Pathogenesis

- HPV in basal cells of squamous epithelium through microtraumatized spots
- Viral replication in spinous layer associated with disturbance of epithelial maturation
- Separated into juvenile and adult groups with unified biological entity, but with differences in clinical course

CLINICAL ISSUES

Epidemiology

- Incidence
 - 4.3 per 100,000 people (USA Data)
 - Increased incidence in lower socioeconomic level
- Age
 - 1st peak: Before 5 years
 - 2nd peak: 20-40 years
- Sex
 - Children
 - Equal gender distribution
 - Adults
 - Male > female (3:2)

Site

- True and false vocal cords, subglottis, and ventricles most often
 - Not uncommon to have multiple squamous papillomas in endolarynx
- Rarely extralaryngeal spread to trachea, bronchi, hypopharynx &/or oropharynx

Presentation

- Presentation is different based on age at initial presentation
- Children
 - Dysphonia and dyspnea

- Hoarseness
- Stridor
- Less frequently, chronic cough and recurrent upper respiratory infections
- Tend to have more aggressive course
 - Multiple papillomas
 - More frequent recurrences
 - Extralaryngeal spread in 30% (trachea, pulmonary)
- Staging and severity scheme developed for more accurate assessment of treatment response
 - Coltrera-Derkay staging and severity scheme
- Adults
 - Dysphonia
 - Hoarseness
 - Tend to have less aggressive course
 - May have multiple squamous papillomas
 - Recurrences are less common
 - Extralaryngeal spread in 16% (trachea, pulmonary)

Endoscopic Findings

- Papillary to exophytic lesion(s)
- 1 or more tumors may be identified

Treatment

- Options, risks, complications
 - HPV vaccine implementation may alter disease by decreasing at-risk population and disease burden
- Surgical approaches
 - Surgical excision, with microdebrider (suction affected tissue)
 - Endolaryngeal procedure by CO₂ laser
- Adjuvant therapy
 - Antiviral drugs, including cidofovir
 - Interferon
 - Antiangiogenic agents
 - Bevacizumab (Avastin) injected into larynx for recurrent papillomatosis

Prognosis

- Unpredictable biologic behavior
- Presence of HPV in apparently normal mucosa acts as virus reservoir and cause of recurrence
- Neonatal squamous papilloma
 - Negative prognostic factor
 - Associated with greater need for tracheostomy
 - Increased likelihood of mortality
 - High proliferation index and aneuploidy may correlate with increased risk of recurrence
- HPV genotypes 11 and 16
 - Associated with more aggressive clinical course
 - Increased frequency of recurrences
- Malignant transformation
 - Tends to develop in patients with history of heavy smoking
 - Identified in 14% of patients with history of previous irradiation
 - Identified in 2% of patients who have not been irradiated
 - Pediatrics: Malignancies develop preferentially in tracheobronchial locations
 - Adults: Malignancies develop preferentially in larynx
- Overall mortality rate 4-14%

Squamous Papilloma

- Death causally related to
 - Asphyxia
 - Pulmonary involvement
 - Carcinomatous transformation

MACROSCOPIC

General Features

- Frequently multiple lesions
- Pedunculated or sessile
- Exophytic branching
- Frequently in clusters
- Pink to reddish
- Lobular surface

Size

- Wide range
- Generally < 1 cm in greatest dimension

MICROSCOPIC

Histologic Features

- Finger-like projections
- Thin fibrovascular cores
- Core lined or covered by squamous epithelium
- Basal and parabasal hyperplasia
 - Usually to mid-portion of squamous epithelium
 - Mitotic activity in this basal/parabasal zone may be increased
- Clusters of koilocytes in upper part of epithelium
 - Crenated, hyperchromatic nucleus
 - Perinuclear halo or clearing
 - Prominent intercellular borders
- Cytologic and nuclear atypia is uncommon
- Architectural disturbance of epithelium is very rare
- Increased mitoses throughout whole epithelium is rare

ANCILLARY TESTS

Immunohistochemistry

- HPV ISH-**positive** staining
- p16 can be used as surrogate marker
 - Will not give specific serotype if p16 is used
 - Stronger nuclear than cytoplasmic reaction
- High Ki-67 proliferative index is associated with increased risk of disease recurrence in pediatric patients

Flow Cytometry

- Detection of DNA aneuploidy seems to predict increased risk of disease recurrence in pediatric patients

In Situ Hybridization

- Nuclear HPV signals in koilocytes

PCR

- Most sensitive method for HPV detection, including different HPV genotypes
- Not used frequently in daily practice (research setting)

DIFFERENTIAL DIAGNOSIS

Solitary Keratinizing Squamous Papilloma

- Develops in adults

- Prominent surface keratinization
- Keratohyaline granules present
- Lack of koilocytes
- Frequently atypical hyperplastic epithelium

Verrucous Carcinoma

- Larger macroscopic lesion
- Prominent superficial keratin layer (hyperkeratosis)
 - Church spire-type hyperkeratosis
- Broad, pushing border of infiltration at epithelial-stromal junction
- Parakeratotic crypting
- Usually a nonmitotically active lesion
 - Mitoses may be seen in basal/parabasal zone
- Shows maturation toward surface
- Lack of koilocytes

Papillary Squamous Cell Carcinoma

- Broad-based to delicate fronds of fibrovascular stroma covered with atypical epithelium
- Very cellular tumor
- Lack of maturation toward surface
- Remarkable cellular pleomorphism
- Increased mitotic figures, identified throughout epithelium
- Atypical mitotic figures
- Invasion into stroma may or may not be present

Verruca Vulgaris

- Very uncommon in larynx
- Lack of branching of fibrovascular cores
- Prominent surface keratinization
- Prominent keratohyaline granules

REPORTING

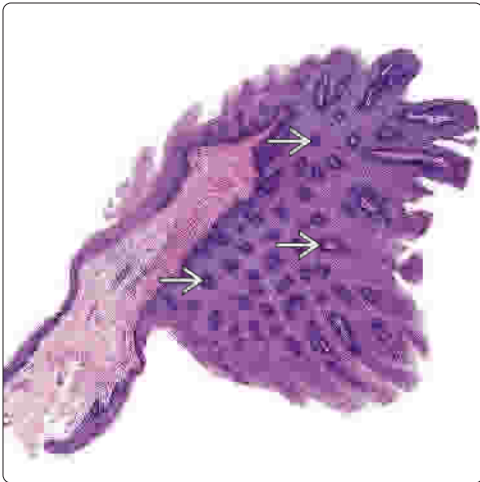
Key Elements to Report

- When premalignant changes (dysplasia) are present, they should be documented

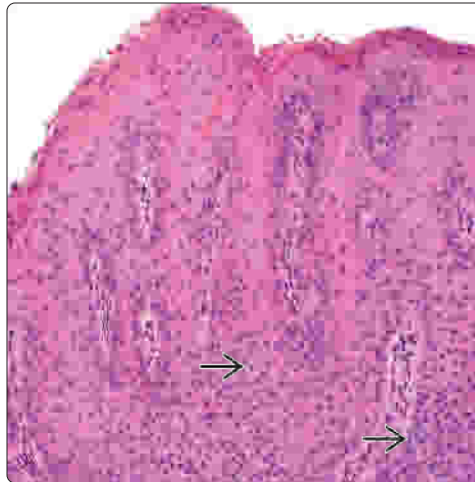
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Squamous Papilloma

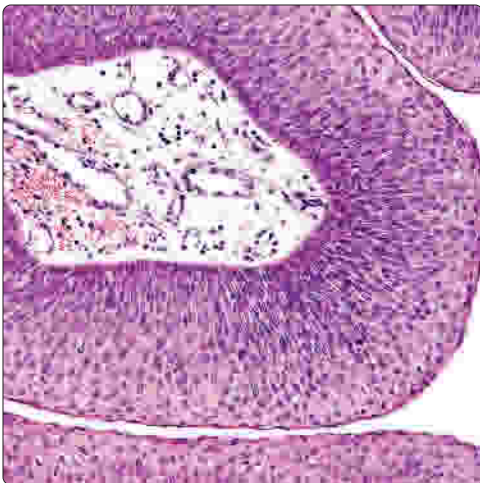


Keratosis at Surface



(Left) There is a large stalk with several papillary projections. However, due to tangential sectioning, they appear as a solid proliferation, with fibrovascular cores noted throughout. **(Right)** These fibrovascular lined spaces show a squamous epithelium associated with keratosis at the surface. There is no significant pleomorphism. Mitoses are seen.

Limited Dysplasia in Squamous Papilloma



High Power of Cytologic Atypia

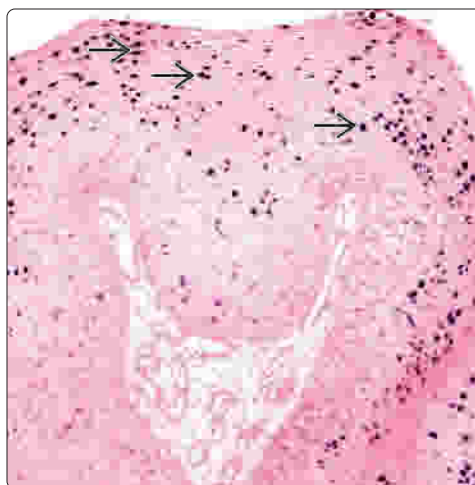


(Left) This squamous papilloma shows mild dysplasia (basal-parabasal cell hyperplasia). The reproducibility of this degree of cytologic atypia is limited, with high intra- and interobserver variability. This lesion shows maturation toward the surface. **(Right)** The squamous epithelium of the papillary projection displays numerous koilocytes on the surface of the epithelial projection. There is also slight parakeratosis on the surface. These changes are within the spectrum of squamous papilloma.

Severe Dysplasia in Squamous Papilloma



ISH to Detect Low-Risk HPV



(Left) Epithelial abnormalities are identified throughout the epithelial thickness, a finding of severe dysplasia. There is limited surface maturation. Mitoses are increased. **(Right)** In situ hybridization for HPV genotypes 6 and 11 shows multiple positive signals in the upper part of the squamous epithelium. In general, ISH is not required to confirm the diagnosis.

Granular Cell Tumor

KEY FACTS

TERMINOLOGY

- Benign tumor of Schwann cell origin, composed of polygonal to spindle cells with abundant granular cytoplasm due to increased number of lysosomes

CLINICAL ISSUES

- Frequent tumor; larynx is involved in ~ 10% of cases
- Mean age: 34 years
- Male < female (1:2)
- Posterior 1/3 of true vocal cord is most common location, with frequent extension into subglottis
- Hoarseness, dysphagia, and cough
- Treatment: Complete but conservative surgery, preserving normal laryngeal function

MACROSCOPIC

- Firm, polypoid, or sessile tumor, usually < 2 cm

MICROSCOPIC

- Poorly circumscribed tumor



- Syncytial pattern is often present
- Sheets, clusters, and nests of neoplastic cells
- Composed of large, rounded, polygonal, or elongated cells with ill-defined borders
- Cytoplasm is eosinophilic, abundant, and coarsely granular
- Pseudoepitheliomatous hyperplasia of surface epithelium
- Dense fibrovascular stroma (desmoplasia)
- Nerves are entrapped within proliferation

ANCILLARY TESTS

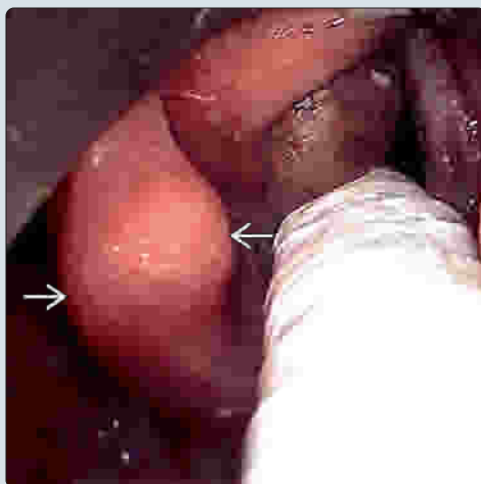
- **Positive:** S100 protein, SOX10, vimentin, NSE, and MBP
- CD68: **Positive** reaction with intracytoplasmic phagolysosomes

TOP DIFFERENTIAL DIAGNOSES

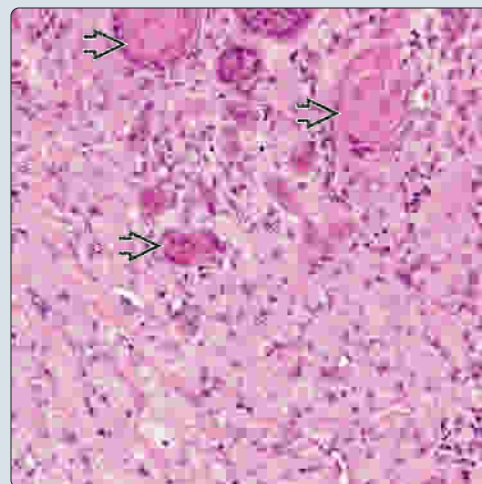
- Squamous cell carcinoma, adult rhabdomyoma, paraganglioma, malignant granular cell tumor, perivascular epithelioid cell tumor



(Left) This endoscopic view shows a laryngeal mass  identified below an intact squamous epithelium. These changes are not specific for a granular cell tumor. (Right) The overlying surface pseudoepitheliomatous hyperplasia (PEH)  is seen to blend imperceptibly with the granular cell proliferation below. This is a characteristic finding, where the PEH is usually limited to the extent of the tumor.

Clinical Photo of Submucosal Larynx Mass

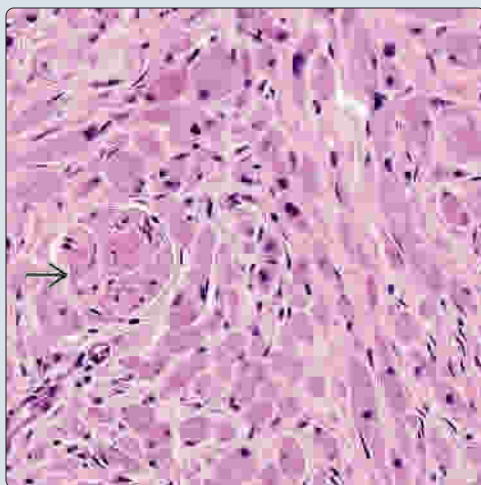


PEH Over Granular Cell Tumor

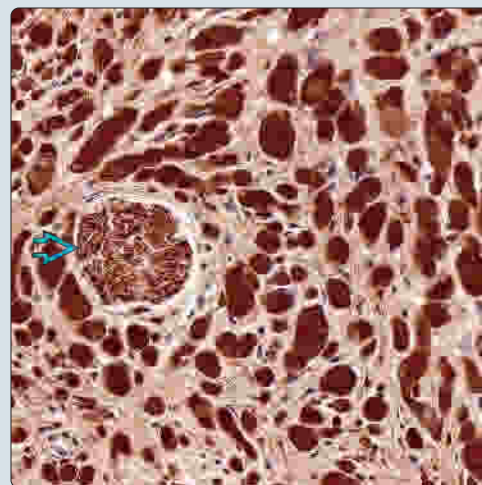


(Left) Large, polygonal cells with abundant granular cytoplasm are seen in this granular cell tumor. Note the entrapped nerve  intimately associated with the proliferation. This is a common finding. (Right) The neoplastic cells show a strong and diffuse cytoplasmic and nuclear reaction for S100 protein in this granular cell tumor. A nerve  serves as a good positive internal control.

Granular Cell Tumor Histology



S100 Protein Reaction



TERMINOLOGY**Abbreviations**

- Granular cell tumor (GCT)

Synonyms

- Myoblastoma, granular cell myoblastoma, Schwann cell tumor, laryngeal xanthoma, Abrikossoff tumor

Definitions

- Benign tumor of Schwann cell origin, composed of polygonal to spindle cells with abundant granular cytoplasm due to increased number of lysosomes

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Frequent tumor; larynx is involved in ~ 10% of cases
- Age
 - Broad age range: 4-70 years
 - Mean: 34 years
 - Uncommon in children
- Sex
 - Male < female (1:2)
- Ethnicity
 - Black people affected more commonly than other races

Site

- Posterior 1/3 of true vocal cord is most common location, with frequent extension into subglottis

Presentation

- Hoarseness, dysphagia, and cough
- Rarely, airway obstruction, difficulty breathing, and stridor
- Multifocal synchronous or metachronous tumors in ~ 10% of patients

Treatment

- Complete but conservative surgery, preserving normal laryngeal function

Prognosis

- Excellent prognosis with low recurrence rate
 - Recurrences in up to 10%

MACROSCOPIC**General Features**

- Firm, polypoid, or sessile tumor
- Usually covered by intact mucosa
- Grayish-yellow cut surface

Size

- Usually < 2 cm

MICROSCOPIC**Histologic Features**

- Poorly circumscribed tumor
- Syncytial pattern is often present
- Sheets, clusters, and nests of neoplastic cells
- Composed of large, rounded, polygonal, or elongated cells with ill-defined borders

- Syncytium is common
- Small hyperchromatic to vesicular nuclei, centrally located
- Cytoplasm is eosinophilic, abundant, and coarsely granular
- Pseudoepitheliomatous hyperplasia of surface epithelium
 - Usually limited to extent of GCT
 - Mimics invasive squamous cell carcinoma
- Dense fibrovascular stroma (desmoplasia), especially in old GCT
- Nerves are entrapped within proliferation
- Cellular atypia, mitoses, and necrosis uncommon
 - If these features are present, it raises suspicion for malignant GCT

ANCILLARY TESTS**Histochemistry**

- PAS-positive, diastase-resistant cytoplasmic granules
- Trichrome differentially highlights granular cells (red) and fibrous stroma (blue)

Immunohistochemistry

- **Positive:** S100 protein, SOX10, vimentin, NSE, and MBP
 - CD68: Positive reaction with intracytoplasmic phagolysosomes
- **Negative:** Cytokeratin, HMB-45, Melan-A, and muscle markers (SMA, desmin, calponin)

DIFFERENTIAL DIAGNOSIS**Squamous Cell Carcinoma**

- Invasive growth, disorganization, single cell infiltration, nuclear pleomorphism, atypical mitoses

Adult Rhabdomyoma

- Well-delineated cell borders between large polygonal, granular, vacuolated cells with abundant glycogen and cross striations
- **Positive:** Desmin, myoglobin

Paraganglioma

- Organoid pattern (zellballen) with **positive** reactions with neuroendocrine markers and sustentacular S100 protein

Malignant Variant of GCT

- Pleomorphism, necrosis, increased mitoses

Perivascular Epithelioid Cell Tumor

- Large, polygonal to epithelioid cells with clear or eosinophilic granular cytoplasm
- **Positive:** HMB-45, Melan-A, SMA; **negative:** S100 protein (cytoplasmic reaction seen in ~ 10%)

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Amyloid (Amyloidoma)

KEY FACTS

TERMINOLOGY

- Benign accumulation of extracellular, acellular, eosinophilic, insoluble protein

CLINICAL ISSUES

- Range: 14-65; mean: 38 years
- Equal gender distribution
- False vocal cord most commonly affected (glottis)
- Progressive hoarseness, often present for extended duration (mean: 19 months)
- Excision, with focus on preserving function
- Good but depends on localized vs. systemic and primary vs. secondary disease
- Recurrences develop in up to 40%, but separation from multifocal disease may be difficult

MACROSCOPIC

- Cut surface shows starch-like, waxy, translucent material below surface

- Up to 4 cm, though mean: 1.6 cm

MICROSCOPIC


- Subepithelial, extracellular, acellular, eosinophilic, homogeneous, amorphous deposits
- Peritheliomatous and periglandular predilection, but randomly distributed within lamina propria
- Foreign body giant cell reaction
- Lymphoplasmacytic infiltrate usually sparse, but can be dense

ANCILLARY TESTS

- Congo red: Amyloid appears red-orange to salmon-pink with apple-green birefringence with polarized light
- Plasma cell light chain restriction (κ or λ) in some cases

TOP DIFFERENTIAL DIAGNOSES

- Mucosa-associated lymphoid tissue (MALT)-lymphoma, vocal cord polyp, lichenoid conjunctivitis, lipoid proteinosis, neuroendocrine carcinomas (larynx or thyroid medullary)

(Left) There is an acellular, extracellular, eosinophilic, homogenous matrix deposition specifically around the glands, characteristic for amyloid. There is an inflammatory infiltrate at the periphery. (Right) H&E shows acellular, eosinophilic, extracellular matrix material with giant cells . There are a few inflammatory cells in the interstitium. This is quite characteristic of amyloid deposition.

Periglandular Amyloid With Inflammation

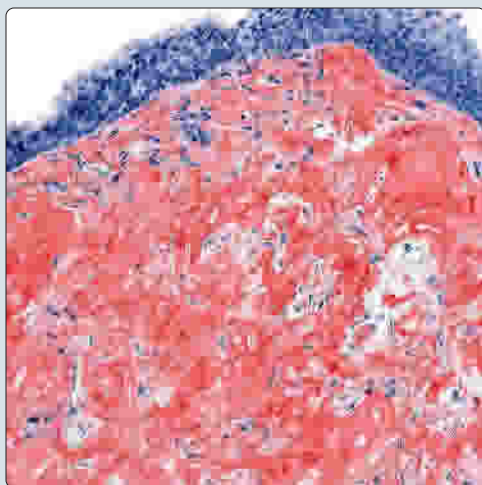


Foreign-Body Giant Cell Reaction

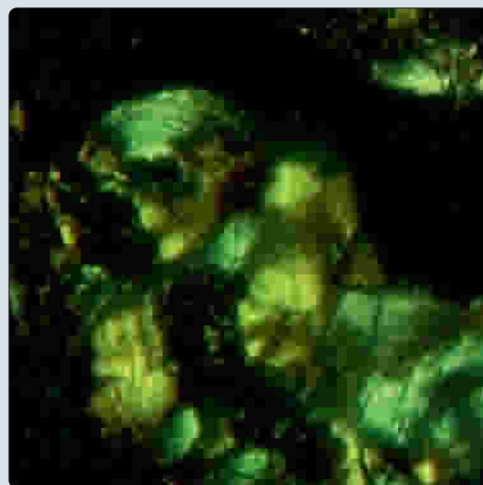


(Left) A positive Congo red stain shows red-orange to salmon-pink material within the stroma of this laryngeal biopsy. There is a different tincture to amyloid than what would be seen in fibrosis. (Right) Positive Congo red stain shows "apple-green" birefringence of amyloid when viewed under polarized light. Note the "rings," which can be highlighted by this technique.

Congo Red Stain Highlights Amyloid



Apple-Green Birefringence of Amyloid With Congo Red



TERMINOLOGY

Synonyms

- Amyloidoma

Definitions

- Benign accumulation of extracellular, acellular, eosinophilic, insoluble protein

ETIOLOGY/PATHOGENESIS

Tumor Associated

- Part of mucosa-associated lymphoid tissue (MALT) or neuroendocrine tumor product

Immunoglobulin

- Generally considered of immunoglobulin origin (immunoproliferative disorder)

Classification

- Acquired systemic amyloidosis (immunocyte dyscrasia, reactive, hereditary)
- Organ limited (immunocyte derived or senile)
- Localized (endocrine organ, plasmacytoma, laryngeal)

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~0.52% of all patients undergoing larynx biopsies
- Age
 - Range: 14-65; mean: 38 years
- Sex
 - Equal gender distribution

Site

- False vocal cord most commonly affected (glottis)
- Multifocal disease elsewhere in upper aerodigestive tract in up to 15% of patients

Presentation

- Progressive hoarseness, often present for extended duration (mean: 19 months)
- Voice changes, including husky voice, dysphagia and changes in phonation

Laboratory Tests

- Quantitative immunoglobulin assay
- Serologic rheumatoid factor tests
- Serum &/or urine electrophoresis to exclude monoclonal gammopathy (Bence-Jones proteins)

Treatment

- Surgical approaches
 - Excision, with focus on preserving function

Prognosis

- Good but depends on localized vs. systemic and primary vs. secondary disease
- Recurrences develop in up to 40%, but separation from multifocal disease may be difficult

MACROSCOPIC

General Features

- Cut surface shows starch-like, waxy, translucent material

Size

- Up to 4 cm; mean: 1.6 cm

MICROSCOPIC

Histologic Features

- Subepithelial, extracellular, acellular, eosinophilic, homogeneous, amorphous deposits
- Peritheliomatous and periglandular predilection, but randomly distributed within lamina propria
- Foreign body giant cell reaction
- Lymphoplasmacytic infiltrate usually sparse, but can be dense
 - Consider undersampled lymphoproliferative disorder (monoclonal if part of MALT)

ANCILLARY TESTS

Histochemistry

- Congo red: Amyloid appears red-orange to salmon-pink with apple-green birefringence with polarized light
- Crystal violet: Metachromatic pink-violet reaction

Immunohistochemistry

- Plasma cell light chain restriction (κ or λ) in some cases
- **Positive:** Amyloid P
- Mixed population of CD3 and CD20 **positive** cells in reactive lymphoid tissue

DIFFERENTIAL DIAGNOSIS

Mucosa-Associated Lymphoid Tissue Lymphoma

- Extranodal marginal zone B-cell lymphoma can be associated with amyloid; light chain restriction

Vocal Cord Polyp

- Hyalinized polyps do not have inflammatory infiltrate or matrix deposition

Ligneous Conjunctivitis

- May be systemic disorder, but **negative** amyloid stains

Tumor Associated

- Larynx neuroendocrine tumor: Amyloid produced but **without** serum calcitonin elevation
- Medullary thyroid carcinoma: Direct invasion into larynx, usually **with** serum calcitonin elevation

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Rhabdomyoma

KEY FACTS

TERMINOLOGY

- Benign, extracardiac soft tissue tumor with skeletal muscle differentiation
 - Extracardiac divided into **adult**, **fetal**, and genital types
 - **FR**: Separated into **myxoid** or **intermediate** types

CLINICAL ISSUES

- **AR**: Male >> female (3-4:1); mean: 6th decade
 - Neck, larynx (supraglottic, glottis), and hypopharynx
- **FR**: Male > female (2:1); ~ 50% within 1st year of life
 - Orbit, tongue, soft palate, periauricular, larynx

MICROSCOPIC

- **AR**
 - Sheets, nests, or lobules
 - Closely packed, large polygonal cells separated by delicate fibrovascular stroma
 - Abundant eosinophilic, granular &/or vacuolated cytoplasm (due to glycogen)

- Vacuolation creates **spiderweb-like** appearance due to radially oriented strands of cytoplasm separating vacuoles

- **FR**
 - Bland, primitive oval to spindled cells with indistinct cytoplasm and slight nuclear hyperchromasia
 - Associated with immature skeletal muscle fibers
 - Large, ganglion cell-like rhabdomyoblasts (cross striations frequent) with vesicular nuclei and prominent nucleoli
 - Infiltration of fat and skeletal muscle
- **Absent**: Nuclear pleomorphism, atypical mitoses, cambium layer (seen in rhabdomyosarcoma)

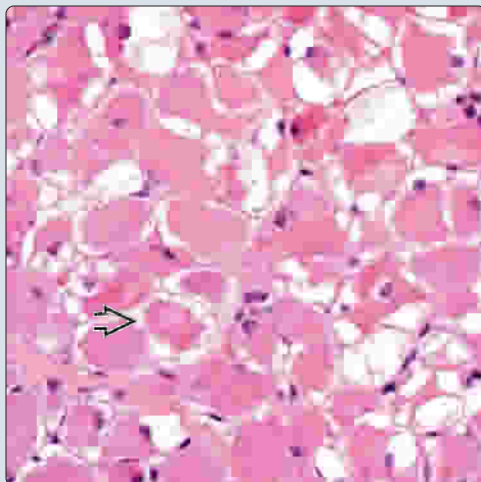
ANCILLARY TESTS

- **Positive**: Desmin, actin, myoglobin, MYOD1

TOP DIFFERENTIAL DIAGNOSES

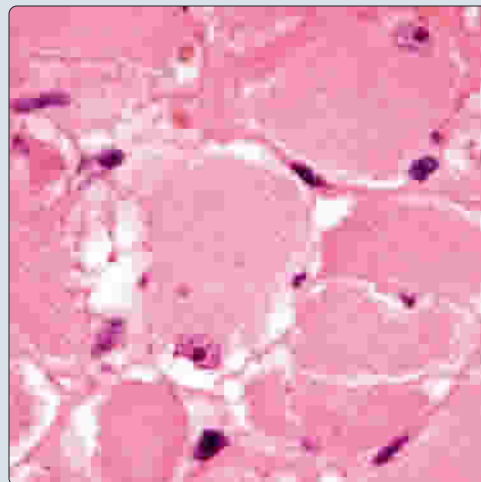
- **AR**: Granular cell tumor, paraganglioma, oncocytoma
- **FR**: Rhabdomyosarcoma, myoepithelioma

Adult Rhabdomyoma: Large Eosinophilic Polygonal Cells

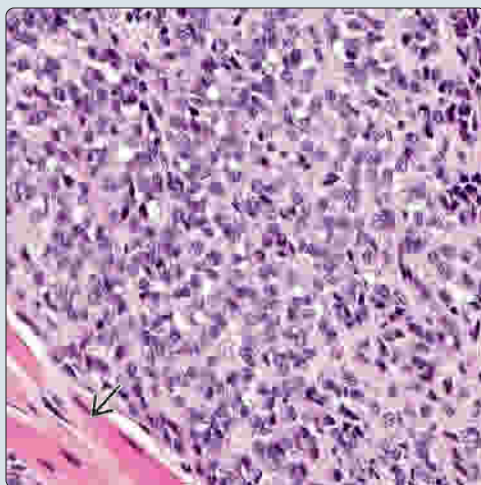


(Left) The characteristic polygonal cells of adult rhabdomyoma (AR) have eosinophilic, vacuolated, granular cytoplasm. The small, hyperchromatic nuclei are mainly peripherally located. Note the spiderweb-like cell [arrow]. (Right) Hematoxylin and eosin at high power demonstrates the characteristic cross striations that can be seen in the cytoplasm of the neoplastic cells. The nuclei are vesicular with a single, prominent nucleolus.

Adult Rhabdomyoma: Cross Striations in Rhabdomyoma

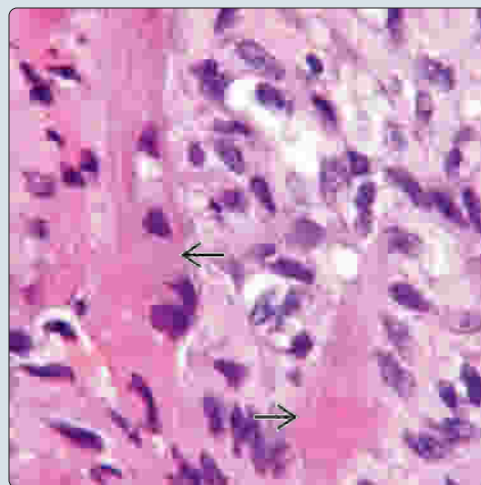


Fetal Rhabdomyoma: Intermediate Type



(Left) This intermediate-type fetal rhabdomyoma (FR) shows mature skeletal muscle [arrow] at the periphery with less differentiated, round to oval cells. There is mild atypia without increased mitoses or necrosis. (Right) There are several large rhabdomyoblast-like cells with prominent striations [arrow] blended with a less differentiated round and oval cell population in this example of a FR, intermediate type.

Fetal Rhabdomyoma: Mixed Skeletal Muscle Differentiation



TERMINOLOGY

Abbreviations

- Adult rhabdomyoma (AR)
- Fetal rhabdomyoma (FR)

Definitions

- Benign, extracardiac soft tissue tumor with skeletal muscle differentiation
- Tumors separated into **cardiac** and **extracardiac** types
 - Extracardiac divided into **adult** (70% in head and neck), **fetal**, and genital types
 - FR: Separated into **myxoid** or **intermediate** (cellular, juvenile, or intermediate type used interchangeably)
 - Genital type develop in middle-aged women in vagina &/or vulva

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Arise from unsegmented mesoderm from 3rd and 4th branchial arches (not from myotomes)

Tumor Association

- Occasional FRs are associated with nevoid basal cell carcinoma syndrome (Gorlin syndrome)
 - Autosomal dominant inheritance with *PTCH* gene mutations (inhibitory receptor in sonic hedgehog signaling pathway)
 - Keratocystic odontogenic tumors, basal cell carcinoma, and abnormalities of bones, skin, nervous, and reproductive system

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very uncommon tumors
- Age
 - **AR**: Mean: 6th decade; range: 16-82 years
 - **FR**: ~ 50% within 1st year of life (congenital), remaining > 15 years
 - Overall median: 4.5 years
- Sex
 - **AR**: Male >> female (3-4:1)
 - **FR**: Male > female (2:1)

Site

- **AR**: Neck, larynx (supraglottic, glottis), and hypopharynx
- **FR**: Orbit, tongue, soft palate, periauricular, larynx, nasopharynx, chest, or abdominal wall

Presentation

- **AR**: Dysphagia, dyspnea, hoarseness
- **FR**: Soft tissue or mucosal mass (orbit, ear, oral cavity)
- Ophthalmologic findings, periauricular mass, difficulty swallowing

Treatment

- Complete surgical excision

Prognosis

- Excellent long-term prognosis

- Larynx tumors lack local aggressiveness or malignant potential
- Recurrences may develop (up to 40%) if incompletely excised

MACROSCOPIC

General Features

- Usually solitary but may be multinodular/multicentric
- **AR**
 - Rounded, lobulated, well-circumscribed, unencapsulated submucosal tumor
 - Tan to grayish red-brown
- **FR**
 - Polypoid to pedunculated when mucosal
 - Well-circumscribed, gray-white, mucoid cut surface

Size

- **AR**: Median: 3 cm; range: 1.5-8.0 cm
- **FR**: Median 3 cm; range 1.0-12.5 cm

MICROSCOPIC

Adult Rhabdomyoma

- Sheets, nests, or lobules
- Closely packed, large polygonal cells separated by delicate fibrovascular stroma
- Abundant eosinophilic, granular, &/or vacuolated cytoplasm (due to glycogen)
 - Vacuolation creates **spiderweb-like** appearance due to radially oriented strands of cytoplasm separating vacuoles
- Small, rounded, centrally, or peripherally located nuclei
- Cytoplasmic cross striations
- Crystalline-like cytoplasmic structures called jackstraw inclusions (rod-like)
- Mitoses, necrosis, and pleomorphism are absent

Fetal Rhabdomyoma

- **Myxoid** type
 - Bland, primitive oval to spindled cells with indistinct cytoplasm and slight nuclear hyperchromasia
 - Associated with immature skeletal muscle fibers
 - Delicate, elongated skeletal muscle cells reminiscent of fetal myotubules
 - Small uniform nuclei
 - Uni- or bipolar eosinophilic cytoplasmic extensions
 - Haphazardly arranged in abundant fibromyxoid stroma
 - Rare mitoses and no atypical forms
 - No pleomorphism or necrosis
- **Intermediate** type
 - Greater degree and greater number of cells with skeletal muscle differentiation
 - Large, ganglion cell-like rhabdomyoblasts with vesicular nuclei and prominent nucleoli
 - Cross striations frequent and easy to identify
 - Interlacing ribbon or strap-like rhabdomyoblasts with abundant deeply acidophilic cytoplasm
 - Broad fascicles of delicate spindled rhabdomyoblasts
 - Infiltration and entrapment of adipose tissue and skeletal muscle
 - Rare areas of fibroblastic proliferation

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
Desmin	Positive	Cytoplasmic	Skeletal muscle cells
Actin-HHF-35	Positive	Cytoplasmic	Skeletal muscle cells
Myoglobin	Positive	Cytoplasmic	Skeletal muscle cells
MYOD1	Positive	Nuclear	In fetal rhabdomyoma only
Myogenin	Positive	Nuclear	Isolated lesional cells (fetal rhabdomyoma); cytoplasmic staining is nonspecific
CK-PAN	Negative		
EMA	Negative		
SOX10	Negative		
CD68	Negative		
Actin-sm	Equivocal	Cytoplasmic	Skeletal muscle cells
S100	Equivocal	Nuclear & cytoplasmic	Skeletal muscle cells may show focal staining
Vimentin	Equivocal	Cytoplasmic	Variable, rare, and focal cells (+) (fetal rhabdomyoma)
GFAP	Equivocal	Cytoplasmic	Rare or focal staining for fetal rhabdomyoma

- Mitoses usually not identified, but when present, can be increased (up to 14/50 HPFs)
- **Absent:** Nuclear pleomorphism, atypical mitoses, cambium layer (seen in rhabdomyosarcoma)
- Transitional forms between myxoid and intermediate types may be seen

ANCILLARY TESTS

Histochemistry

- PAS(+), diastase-resistant glycogen granules
- PTAH highlights cross striations and crystals

Immunohistochemistry

- **Positive** for skeletal muscle markers: Desmin, myoglobin, MYOD1

Genetic Testing

- Reciprocal translocation of chromosome 15 and 17
- Variety of changes in 10q

Electron Microscopy

- Alternating thick and thin myofilaments
- Condensation of rudimentary myofibrils (hypertrophied Z bands)
- Variable amount of glycogen and mitochondria associated with filaments

DIFFERENTIAL DIAGNOSIS

Granular Cell Tumor

- Pseudoepitheliomatous hyperplasia; indistinct cellular borders, lacking vacuolization; S100 protein (+)

Paraganglioma

- Organoid pattern; **positive** for neuroendocrine markers and sustentacular S100 protein

Oncocytoma

- Lacking vacuolization and cross striations

Rhabdomyosarcoma

- Infiltrative and destructive; usually not well circumscribed
- Generally are deep lesions rather than superficial tumors
- Nuclear pleomorphism, increased mitoses (including atypical forms), and necrosis easily identified
- Muscle markers (+) but myogenin stronger and more diffuse; Ki-67 increased

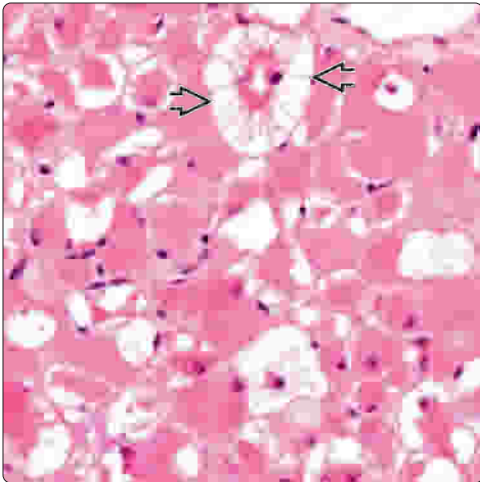
Myoepithelioma

- Spindled cell proliferation but tends to be well circumscribed, lacking significant atypia
- May have myxoid matrix
- **Positive** with epithelial and myoepithelial markers: CK-PAN, p63, S100 protein, SMA; **negative** with myoglobin, myogenin, and MYOD1

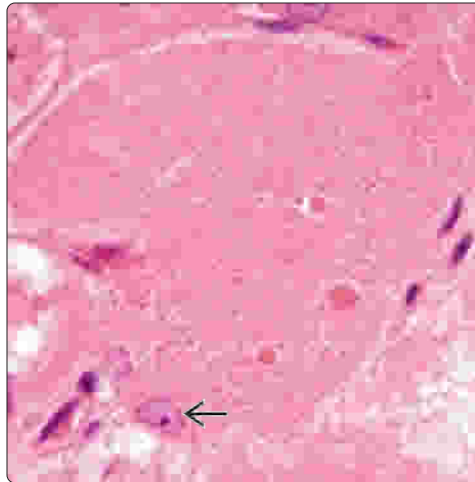
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Adult Rhabdomyoma: Spiderweb-Like Cell

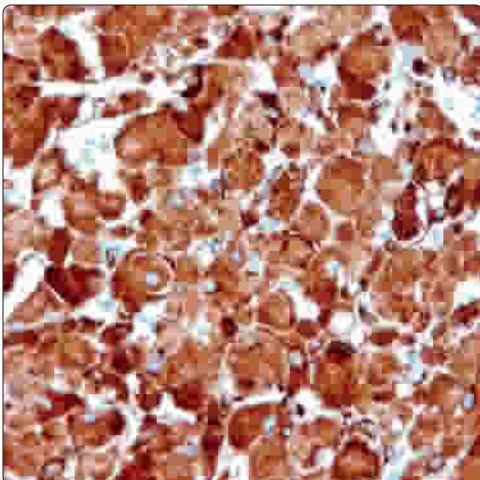


Adult Rhabdomyoma: Cytoplasmic Cross Striations

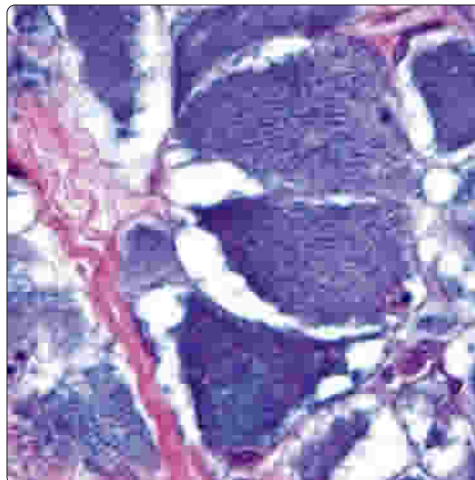


(Left) The characteristic polygonal cells have a eosinophilic, vacuolated, granular cytoplasm. The small, hyperchromatic nuclei are mainly peripherally located. Note the spiderweb-like cell [X]. (Right) This oil immersion photograph demonstrates numerous cross striations within the cytoplasm of a large polygonal cell from an AR. The nucleus [X] is vesicular and off to the side.

Adult Rhabdomyoma: Desmin Immunoreactivity

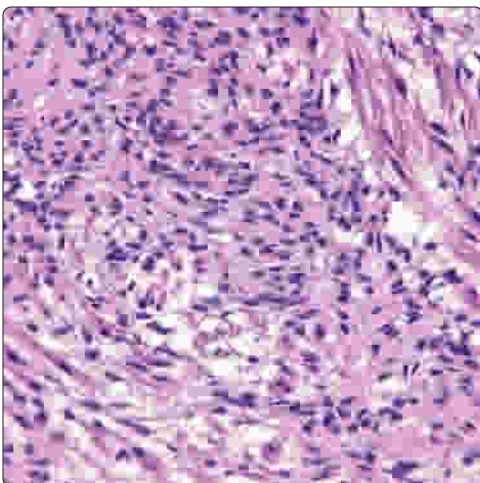


Adult Rhabdomyoma: PTAH Highlights Cross Striations

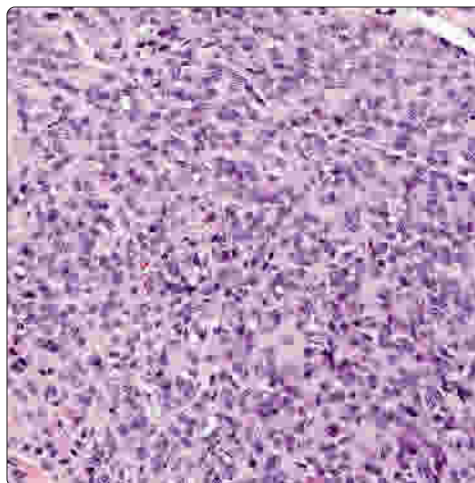


(Left) Desmin demonstrates strong and diffuse cytoplasmic reactivity, characteristic for a rhabdomyoma. This is an example of an AR, but similar reactivity is seen in fetal rhabdomyoma. (Right) PTAH stain highlights the cross striations within the cytoplasm of the muscle cells, creating a fingerprint-like appearance within the cytoplasm.

Fetal Rhabdomyoma: Intermediate Type With Spindled Cells



Fetal Rhabdomyoma: Primitive Round to Oval Cells



(Left) There are fascicles of relatively uniform spindled cells in this example of an intermediate-type FR. The nuclei are bland and uniform with coarse chromatin. Mitoses are absent. (Right) This field demonstrates a sheet of primitive round to oval spindled cells that comprise this FR, intermediate type. There are no pleomorphism, mitoses, or necrosis features helpful in the separation from rhabdomyosarcoma.

KEY FACTS

TERMINOLOGY

- Benign mesenchymal neoplasm of cartilaginous supporting structures of larynx

ETIOLOGY/PATHOGENESIS

- Endochondral ossification of laryngeal hyaline cartilages at points of mechanical stress/tension (muscle insertion points)
- Ischemic change associated with malignant transformation

CLINICAL ISSUES

- Present about a decade earlier than chondrosarcoma: Mean, 5th decade
 - Chondrosarcomas >> chondroma (17:1)
- Male > female (2-3:1)
- Slowly progressive obstruction
- Anterior surface of posterior lamina of cricoid cartilage
- Complete but conservative resection (includes endoscopic laser)

IMAGING

- CT accurately demonstrates size, extent of tumor, and whether "destructive" growth is present

MACROSCOPIC

- Adequate sampling to exclude chondrosarcoma
- Firm, glassy, blue-white cut surface
- By definition, < 2 cm in diameter



MICROSCOPIC

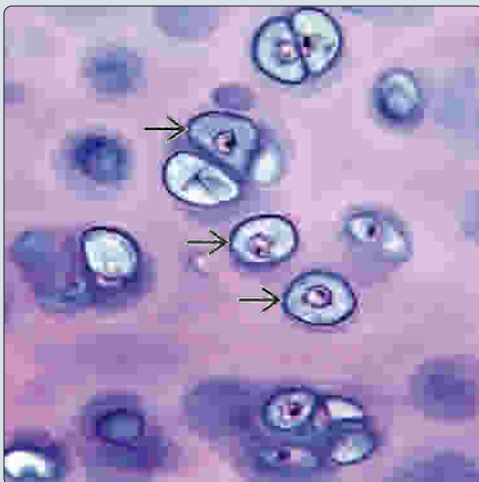
- Hyaline cartilage with low cellularity
- Evenly distributed, well-defined, lobular pattern
- Individual, bland chondrocytes within lacunae

TOP DIFFERENTIAL DIAGNOSES

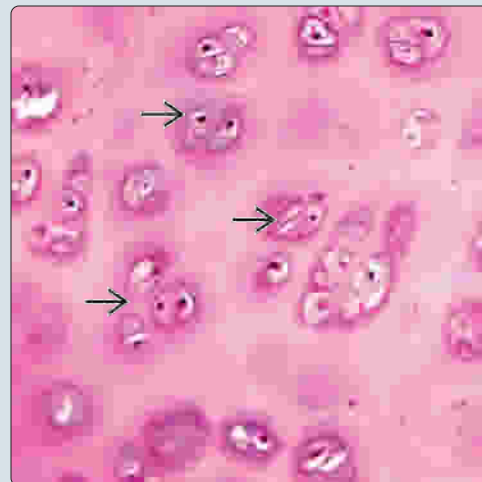
- Chondrosarcoma
- Pleomorphic adenoma
- Chondrometaplasia
- Tracheopathia osteochondroplastica

Slightly Increased Cellularity

(Left) Note the relative paucity of cells, each lacunae containing only a single cell , with a normal-appearing nucleus. There is no clustering or disorganization. **(Right)** Hematoxylin and eosin shows slightly increased cellularity  but no cytologic atypia, binucleation, or cluster disarray. The cellular features in this case are characteristic of a chondroma.

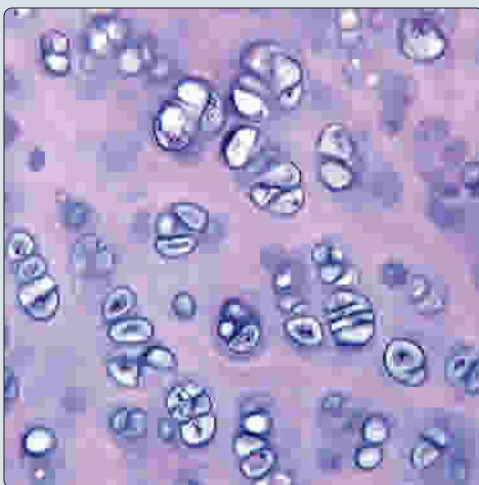


Increased Cellularity Without Atypia

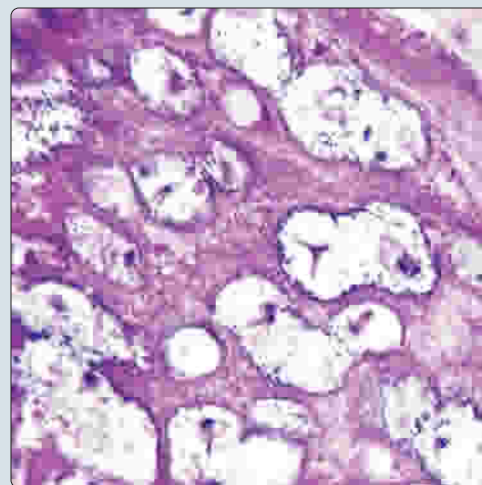


No Cluster Disarray or Pleomorphism

(Left) There is increased cellularity but no disarray, binucleation, or atypia. This case would be difficult to separate from a low-grade chondrosarcoma without radiographic and macroscopic correlation. **(Right)** This chondroma shows ischemic change, with blue, granular material in the cytoplasm of the cell and in the adjacent matrix.



Ischemic Change in Chondroma



TERMINOLOGY

Synonyms

- Osteochondroma

Definitions

- Benign mesenchymal neoplasm of cartilaginous supporting structures of larynx

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Endochondral ossification of laryngeal hyaline cartilages at points of mechanical stress/tension (muscle insertion points)
- With ischemic change, malignant transformation is more likely to develop

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare: < 1% of laryngeal tumors
 - Chondrosarcomas > > chondroma (17:1)
- Age
 - Mean: 5th decade (~ 10 years younger than chondrosarcoma)
- Sex
 - Male > female (2-3:1)

Site

- Anterior surface of posterior lamina of cricoid cartilage
 - Thyroid, arytenoid, and epiglottic cartilages infrequently affected

Presentation

- Slowly progressive obstruction
- Subglottic tumors: Dyspnea, hoarseness, and stridor
- Supraglottic tumors: Hoarseness, dyspnea, dysphagia, and odynophagia
- Neck mass (thyroid cartilage specifically)

Treatment

- Complete but conservative resection (includes endoscopic laser)
 - If cricoid ring is destroyed, laryngeal stabilization is required
- Very important to adequately sample tumors to exclude chondrosarcoma

Prognosis

- Excellent, although recurrence may develop
 - Possibility that original lesion was underdiagnosed chondrosarcoma
 - Up to 10% recurrence; develops many years after resection (mean: 9 years)
- Transformation to chondrosarcoma (~ 7%)
- Concurrent chondrosarcomas (up to 60%), especially if ischemic change in chondroma

IMAGING

General Features

- CT accurately demonstrates size, extent of tumor, and whether "destructive" growth is present
 - Hypodense, well-circumscribed mass with regular margins centered in cartilage
 - Minimal calcifications are present
- MR better for tumor to soft tissue relationship and extent of tumor than CT

MACROSCOPIC

General Features

- Firm, glassy, blue-white cut surface

Size

- By definition, < 2 cm in diameter

MICROSCOPIC

Histologic Features

- Hyaline cartilage with low cellularity
- Evenly distributed, well-defined, lobular pattern
- Individual, bland chondrocytes within lacunae
- Cells with single, uniform, small hyperchromatic nuclei surrounded by clear to eosinophilic cytoplasm
- Exceptionally, binucleated chondrocytes
- Calcification and ossification may be seen
- Ischemic change may herald malignant transformation

DIFFERENTIAL DIAGNOSIS

Chondrosarcoma

- On biopsy, differentiation may be impossible
 - Use "cartilaginous lesion without definitive evidence of malignancy, requiring examination of complete lesion" as diagnosis
- Bone destruction or invasion, increased cellularity, loss of organization, lobular disarray, increased pleomorphism, multinucleation

Chondrometaplasia

- Ill-defined, submucosal, elastic-rich cartilage nodule affecting vocal cord, without cartilaginous connection

Tracheopathia Osteochondroplastica

- Multiple submucosal nodules, attached to cartilage

Pleomorphic Adenoma

- Epithelial/myoepithelial components blended with chondromyxoid stroma

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Inflammatory Myofibroblastic Tumor

KEY FACTS

TERMINOLOGY

- Distinctive lesion composed predominantly of myofibroblastic cells with variable admixture of inflammatory cells, including mature lymphocytes, histiocytes, plasma cells, eosinophils, and extracellular collagen

CLINICAL ISSUES

- Predominantly soft tissue and visceral tumor that may occur in mucosa of upper aerodigestive tract
- Upper aerodigestive tract inflammatory myofibroblastic tumors (IMTs) rare
 - Larynx most common: True vocal cord (glottis) most common > supraglottis, subglottis
- Conservative surgical resection, including local excision by laser removal or via laryngoscopic techniques
- Conservative resection usually curative
- Targeted therapy using ALK inhibitor crizotinib has shown promising results in ALK-translocated IMTs

MICROSCOPIC

- Cellular proliferation loosely arranged with storiform to fascicular growth patterns and edematous myxoid to fibromyxoid stroma, prominent vascularity, and variable inflammatory cell infiltrate
- Spindle-shaped or stellate, enlarged round to oblong nuclei, inapparent to prominent eosinophilic nucleoli, and abundant basophilic fibrillar-appearing cytoplasm; intranuclear inclusions may be seen

ANCILLARY TESTS

- Vimentin, actins (smooth muscle, muscle specific) **positive**
- Cytoplasmic reactivity for ALK1 can be seen; ALK1 reactivity also present in intranuclear inclusions
- ALK gene rearrangements
 - 50-70% of cases in children and young adults have cytogenetic rearrangements (chromosome band 2p23)
 - Such rearrangements are uncommon in adults > 40 years

Laryngectomy

(Left) Laryngeal inflammatory myofibroblastic tumor (IMT) appears as a polypoid and nodular lesion. Conservative surgical excision is usually curative, but this patient's lesion recurred multiple times, necessitating a laryngectomy. **(Right)** Laryngeal IMT appears as a polypoid lesion with an intact surface epithelium and a submucosal loosely cellular proliferation with storiform to fascicular growth and edematous myxoid stroma. These findings are similar to those of nodular fasciitis.

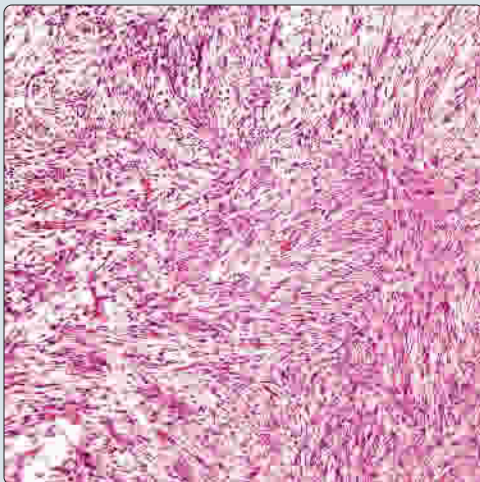


Laryngeal Inflammatory Myofibroblastic Tumor, Polypoid Lesion

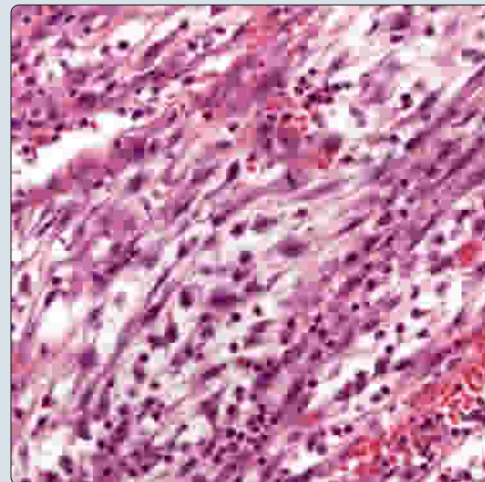


Laryngeal Inflammatory Myofibroblastic Tumor, Storiform Growth

(Left) At higher magnification, the histologic similarities to nodular fasciitis are seen, including loosely arranged spindle cell proliferation with storiform to fascicular growth and myxoid-appearing stroma. **(Right)** Myofibroblasts are predominantly spindle-shaped with elongated nuclei and abundant eosinophilic-appearing fibrillar cytoplasm. An associated myxoid stroma with mixed inflammatory cell infiltrate is present.



Spindle-Shaped Myofibroblasts



TERMINOLOGY

Abbreviations

- Inflammatory myofibroblastic tumor (IMT)

Synonyms

- Inflammatory (myofibroblastic) pseudotumor
- Plasma cell granuloma
- Plasma cell pseudotumor
- Pseudosarcomatous (myofibroblastic) lesions/tumor

Definitions

- Distinctive lesion composed predominantly of myofibroblastic cells with variable admixture of chronic inflammatory cells and extracellular collagen
 - Predominantly soft tissue and visceral tumor that may occur in mucosa of upper aerodigestive tract

ETIOLOGY/PATHOGENESIS

Etiology

- Unknown
- No specific link to tobacco smoking, trauma (e.g., traumatic intubation), human herpesvirus 8 or Epstein-Barr virus

CLINICAL ISSUES

Epidemiology

- Age
 - Upper aerodigestive tract IMT
 - Wide age range, including pediatric population, but more common in adult populations
 - Laryngeal IMT
 - Median age: 59 years
- Sex
 - Laryngeal IMT
 - Male > female

Site

- Upper aerodigestive tract IMTs rare
 - Larynx most common
 - True vocal cord (glottis) most common > supraglottis, subglottis
 - Nonlaryngeal sites include oral cavity, tonsil, parapharyngeal space, sinonasal tract, salivary glands, and trachea

Presentation

- Laryngeal IMTs
 - Hoarseness, stridor, dysphonia, foreign body sensation in throat
 - Duration of symptoms range from days to months
- Upper aerodigestive tract IMTs
 - Painless mass (\pm ulceration), nasal obstruction, epistaxis, headache, dysphagia
- Soft tissue and visceral IMTs
 - Constitutional &/or systemic signs and symptoms (not usually component of upper aerodigestive tract IMTs)
 - Fever, weight loss, pain, malaise, anemia, thrombocytosis, polyclonal hyperglobulinemia, elevated erythrocyte sedimentation rate

Treatment

- Surgical approaches
 - Conservative surgical resection, including local excision by laser removal or via laryngoscopic techniques
- Drugs
 - Corticosteroid and nonsteroidal anti-inflammatory agents have been used, resulting in regression in some patients
 - Targeted therapy using ALK inhibitor crizotinib has shown promising results in ALK-translocated IMTs

Prognosis

- Conservative resection usually curative
- Rarely, tumors recur following surgical resection
 - Recurrence rate of ~ 25% reported for extrapulmonary IMTs
 - Rare examples of extrapulmonary (non-head and neck) IMTs metastasize
- Difficult to predict on basis of pathologic features which IMTs may behave more aggressively
 - No correlation between behavior and tumor size, nuclear atypia, mitotic activity, necrosis
 - Aggressive behavior may correlate to round cell transformation characterized by
 - Sheets of round to epithelioid cells with vesicular nuclei, prominent nucleoli, amphophilic to eosinophilic cytoplasm, increased mitotic activity, including atypical mitoses, myxoid stroma, and prominent neutrophilic infiltrate
 - Distinct nuclear membrane or perinuclear pattern of ALK staining
 - *RANBP2-ALK* fusion detected by reverse-transcription PCR; to date, such changes reported in IMTs located within abdomen arise from omentum or mesentery; terminology of epithelioid inflammatory myofibroblastic sarcoma suggested for this lesion conveying malignant behavior

MACROSCOPIC

General Features

- Polypoid, pedunculated, or nodular firm lesion with smooth appearance and fleshy to firm consistency
- IMTs of upper aerodigestive tract usually present as solitary lesions

Size

- 0.4-3.0 cm in greatest dimension

MICROSCOPIC

Histologic Features

- Polypoid and unencapsulated submucosal loosely cellular proliferation of spindle-shaped to stellate cells
- Cellular proliferation loosely arranged with storiform to fascicular growth patterns and edematous myxoid to fibromyxoid stroma, prominent vascularity, and variable inflammatory cell infiltrate
 - Mature lymphocytes, histiocytes, plasma cells, eosinophils, and scattered polymorphonuclear leukocytes

Inflammatory Myofibroblastic Tumor

Myofibroblasts

- Spindle-shaped or stellate, enlarged round to oblong nuclei, inapparent to prominent eosinophilic nucleoli, and abundant basophilic fibrillar-appearing cytoplasm
- Myofibroblasts may also appear
 - Epithelioid or histiocytoid with round to oval nuclei, prominent nucleoli, and abundant basophilic fibrillar-appearing cytoplasm
 - Axonal (spider-like) cells with elongated nuclei, inapparent nucleoli, and long cytoplasmic extensions creating cells with bipolar to multipolar appearance (tadpole-like)
- In all examples, low nuclear:cytoplasmic ratio
- Intracellular inclusions may be seen
- Increased mitotic figures are common and may be numerous, but atypical mitoses not usually seen
- Marked nuclear pleomorphism and necrosis not present

Stroma

- Varies from edematous myxoid background to fibromyxoid and more fibrous stroma
- Fibrillar-appearing stroma resembling neurofibrillary matrix may rarely be seen
- Vascular component varies, including widely dilated medium-sized vascular channels to narrow, slit-like blood vessels
 - Can be obscured by myofibroblasts and inflammatory cells

Surface Epithelium

- May be intact and unremarkable to ulcerated and hyperplastic in appearance
- Myofibroblastic proliferation approximates but typically does not involve surface epithelium
- Reactive epithelial atypia may be seen
 - Significant epithelial dysplasia (i.e., moderate to severe dysplasia), carcinoma in situ, and invasive squamous carcinoma not present

ANCILLARY TESTS

Immunohistochemistry

- Strong diffuse cytoplasmic immunoreactivity for vimentin
- Variable immunoreactivity for smooth muscle actin, muscle-specific actin, calponin, and caldesmon
- Desmin immunoreactivity may be seen
- Reactivity for ALK can be seen corresponding to presence of ALK rearrangements
 - ALK reactivity is cytoplasmic; intranuclear inclusions may be ALK(+)
 - Wide range of ALK positivity reported varying from 36-60% of cases
 - ALK lacks specificity and sensitivity and shows imperfect correlation to *ALK* mutations, and different fusion partners may result in different patterns of ALK immunoreactivity
- Cytokeratin, S100 protein, HMB-45, myoglobin, myogenin, MYOD1, CD34, CD117 (c-kit) usually **negative**

Genetic Testing

- *ALK* gene rearrangements and expression seen in IMTs

- In children and young adults, 50-70% of cases often contain clonal cytogenetic rearrangements involving chromosome band 2p23 that fuse 3' kinase region of *ALK* gene with various partner genes including: *TPM3*, *TPM4*, *CLTC*, *RANBP2*, and *ATIC*
 - Such rearrangements are uncommon in adults > 40 years
- Gene rearrangements and protein activation restricted to myofibroblastic component of IMTs
 - Inflammatory cell component lacks gene rearrangements or expression of ALK protein
- Presence of immunohistochemical expression of ALK C-terminal end in myofibroblastic component of IMTs and low to absent detection of ALK protein in nonneoplastic myofibroblasts represent strong evidence for oncogenic activation mechanism in IMTs

DIFFERENTIAL DIAGNOSIS

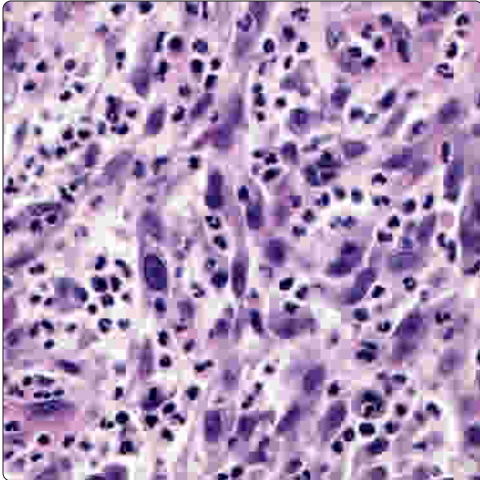
Spindle Cell Squamous Carcinoma

- Histologically high-grade variant of squamous cell carcinoma
- Usually densely cellular, composed of malignant spindle-shaped &/or pleomorphic cell population with increased mitotic figures and atypical mitoses
- Intraepithelial dysplasia (moderate to severe) &/or invasive differentiated squamous cell carcinoma may be present
 - Surface ulceration is common, and differentiated squamous cell component may not be present
- Cytokeratin immunoreactivity present in > 70% of cases

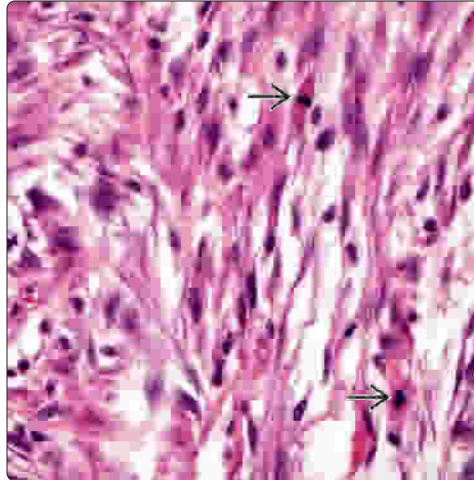
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Myofibroblasts and Inflammatory Cells

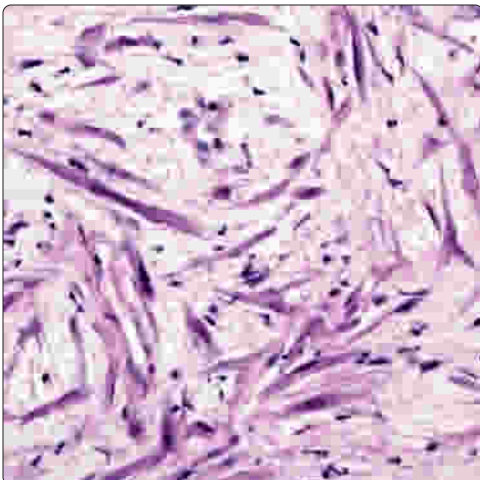


Spindle-Shaped Myofibroblasts

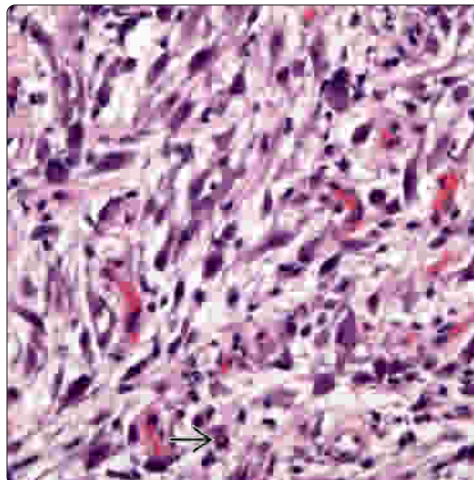



(Left) Myofibroblasts vary in appearance from case to case and in the same case. The myofibroblasts include spindle-shaped to stellate cells with round to oblong nuclei, inapparent to prominent eosinophilic nucleoli, and ample basophilic fibrillar cytoplasm; background inflammatory cell infiltrate is present. (Right) H&E shows spindle-shaped myofibroblasts with elongated nuclei and abundant eosinophilic- to basophilic-appearing fibrillar cytoplasm and scant inflammatory cell infiltrate. A mitotic figure is present .

Myofibroblasts With Axonal-Like Extensions

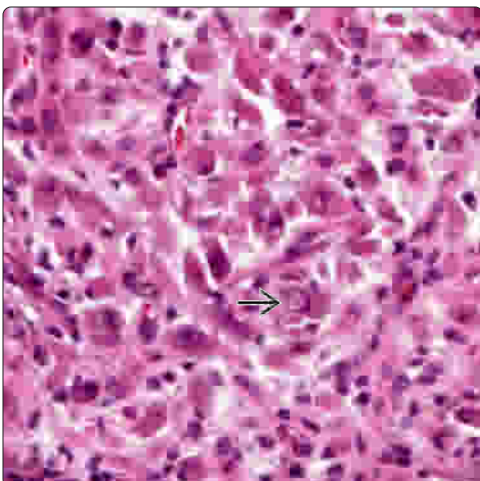


Spindle and Epithelioid Myofibroblasts

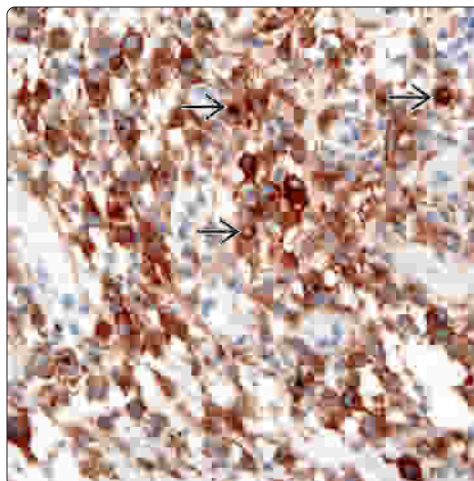




(Left) Myofibroblasts may appear axonal (spider-like) with long cytoplasmic extensions, creating cells with bipolar to multipolar (tadpole-like) appearance. Variable admixed inflammatory cell infiltrate is present. Inflammatory cell component may vary considerably from case to case. (Right) Spindle-shaped and epithelioid myofibroblasts have abundant basophilic-appearing cytoplasm, some with axonal-like extensions, and some with rhabdoid or plasmacytoid features. Intranuclear inclusion is present .

Epithelioid Myofibroblasts With Inclusions



ALK1 Reactivity



(Left) The myofibroblasts may appear epithelioid in appearance with round to oval nuclei, prominent eosinophilic nucleoli, and abundant basophilic- to eosinophilic-appearing fibrillar cytoplasm. In addition, an intranuclear inclusion  is present, a rather characteristic but not pathognomonic finding. (Right) Immunoreactivity for ALK1 is a helpful diagnostic finding in IMTs. The lesional cells show the presence of intracytoplasmic ALK staining; intranuclear inclusions  are also immunoreactive for ALK1.

Paraganglioma

KEY FACTS

TERMINOLOGY

- Benign neuroendocrine tumor arising from either superior or inferior laryngeal paraganglia, composed of chief and sustentacular cells arranged in organoid pattern

CLINICAL ISSUES

- Very rare sporadic predominantly supraglottic laryngeal tumor
 - Supraglottis (82%)
- Mean age at presentation: 47 years
 - Range: 5-83 years
- Female > male (3:1)
- Hoarseness is major symptom
- Surgery yields excellent prognosis
 - ~ 20% of patients may develop local recurrences

MICROSCOPIC

- Rounded, submucosal tumor

- Paraganglia (chief) and sustentacular cells form alveolar (**zellballen**) pattern
- 2 cell types
 - Chief cells have eosinophilic, finely granular cytoplasm, and centrally located nuclei
 - Cellular pleomorphism may be present
 - Sustentacular cells are inconspicuous spindle-shaped at periphery of cell balls
- Highly vascular fibrous stroma

ANCILLARY TESTS

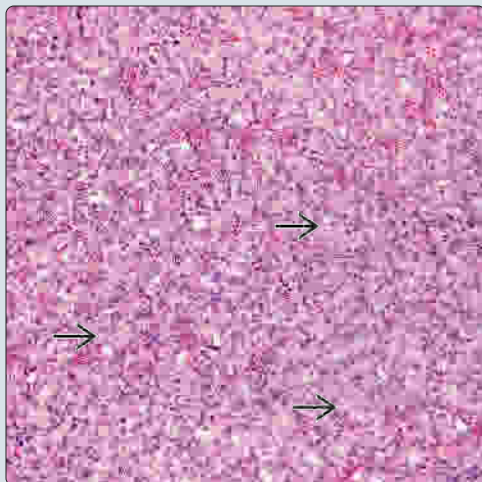
- Paraganglia cells: **Positive:** Synaptophysin, chromogranin-A, CD56
- Sustentacular cells: **Positive:** S100 protein, GFAP

TOP DIFFERENTIAL DIAGNOSES

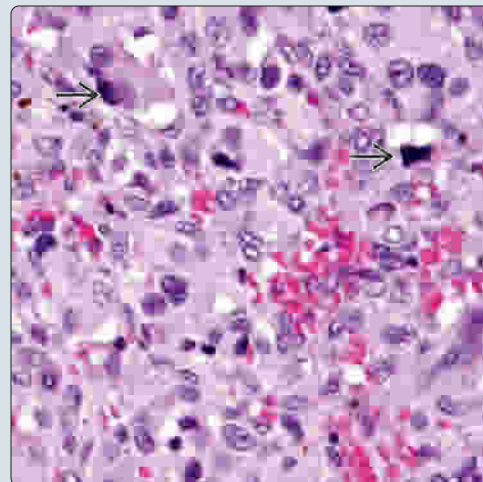
- Neuroendocrine tumors: Typical and atypical carcinoid
- Medullary thyroid carcinoma
- Mucosal melanoma; metastatic renal cell carcinoma

Zellballen Architecture With Small Nests

(Left) Hematoxylin and eosin shows the characteristic alveolar pattern (zellballen) of paraganglioma. Small nests of cells [] are surrounded by a fibrovascular, richly vascularized stroma. (Right) Hematoxylin and eosin shows focal nuclear pleomorphism [] of the chief cells in this paraganglioma with a nested pattern of growth.

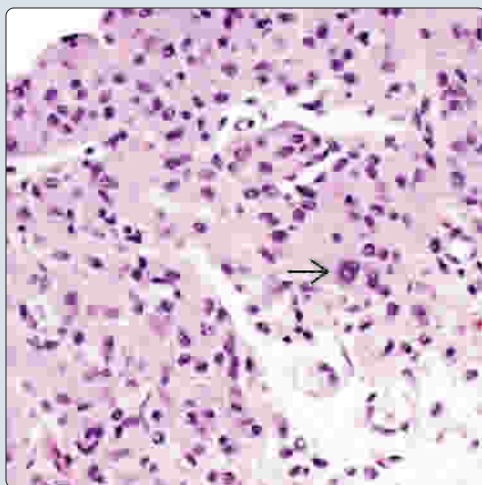


Isolated Pleomorphic Nuclei

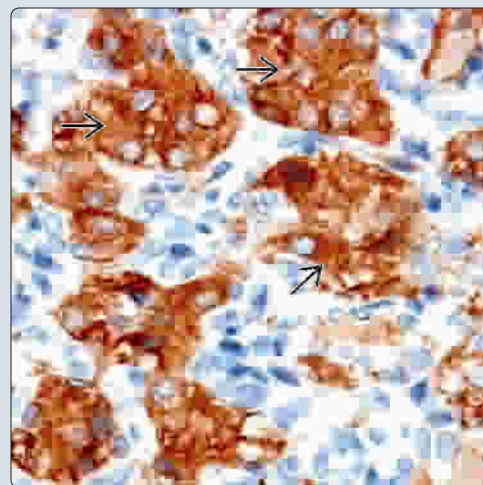


Vague Alveolar Pattern With Pleomorphism

(Left) There is a vague alveolar or zellballen architecture with rare cells [] showing pleomorphism. There is granular, blue cytoplasm surrounding round to oval nuclei. (Right) Synaptophysin shows strong and diffuse immunoreactivity of the chief cells []. There is no reactivity of the supporting sustentacular cells (which would stain with S100 protein).



Synaptophysin Immunoreactivity



TERMINOLOGY**Synonyms**

- Glomus tumor, chemodectoma, nonchromaffin paraganglioma

Definitions

- Neuroendocrine tumor arising from either superior or inferior laryngeal paraganglia, composed of chief and sustentacular cells arranged in organoid pattern

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Very rare laryngeal tumor
- Age
 - Mean: 47 years; range: 5-83 years
- Sex
 - Female > male (3:1)

Site

- Supraglottis (82%)
- Subglottis (15%); glottis (3%)
- Rarely multicentric

Presentation

- Hoarseness is major symptom
- Dysphagia, dyspnea, stridor, sore throat

Treatment

- Surgical approaches
 - Excision with external approach
 - Intraoperative bleeding may be significant

Prognosis

- Excellent
- ~ 20% of patients may develop local recurrences, 1-16 years after excision

MACROSCOPIC**General Features**

- Rounded submucosal mass
- Cut surface is homogeneous or nodular, pink to tan and dark red

Size

- Range: 0.5-6.0 cm

MICROSCOPIC**Histologic Features**

- Nests of tumor cells are surrounded by highly vascular fibrous tissue
- 2 cell types
 - Chief and sustentacular cells form alveolar (**zellballen**) pattern
- Paraganglia (chief) cells have eosinophilic, finely granular cytoplasm, and centrally located nuclei
 - Cellular pleomorphism may be present but is prognostically unimportant
- Sustentacular cells are inconspicuous and spindle-shaped at periphery of cell balls
 - Only identified by S100 protein or GFAP immunohistochemistry
- Rare mitoses

DIFFERENTIAL DIAGNOSIS**Neuroendocrine Tumors**

- Both typical and atypical carcinoid
- Organoid, trabecular, or glandular patterns
- **Positive:** Both neuroendocrine and epithelial markers

Medullary Thyroid Carcinoma

- Multiple patterns of growth, often with amyloid deposition
- **Positive:** Calcitonin, TTF-1, CEA-m, synaptophysin, chromogranin-A; **negative:** S100 protein

Mucosal Melanoma

- Multiple patterns of growth
- **Positive:** S100 protein, HMB-45, melan-A

Metastatic Renal Cell Carcinoma

- Organoid pattern
- **Positive:** Keratin, vimentin, CD10, pax-2, renal cell carcinoma marker
- **Negative:** Chromogranin-A, S100 protein

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Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
Chromogranin-A	Positive	Cytoplasmic	Chief/paraganglia cells
Synaptophysin	Positive	Cytoplasmic	Chief/paraganglia cells
CD56	Positive	Cell membrane	Chief/paraganglia cells
NSE	Positive	Cytoplasmic	Chief/paraganglia cells
S100	Positive	Nuclear & cytoplasmic	Sustentacular cells
GFAP	Positive	Cytoplasmic	Sustentacular cells
CK-PAN	Negative		

KEY FACTS

TERMINOLOGY

• Keratinizing dysplasia

- Potentially reversible (qualitative) alteration in malignant direction in appearance of epithelial cells with increased likelihood to progress to squamous cell carcinoma

• Carcinoma in situ (CIS)

- Classically defined as malignant alteration characterized by cellular dysplasia involving entire thickness of surface epithelium without violation of basement membrane
- Considered irreversible process that will progress to invasive carcinoma if left untreated

MICROSCOPIC

• Keratinizing dysplasia



- Most common type of dysplasia in upper aerodigestive tract (UADT)
- Similar grading as nonkeratinizing dysplasia (i.e., mild, moderate, and severe) depending on degree and extent of cellular and maturation alterations

- Definition of keratinizing severe dysplasia, especially laryngeal and oral cavity, broader, more heterogeneous, and less reproducible than nonkeratinizing dysplasias
- Invasive carcinoma may develop in epithelium, showing dysplasia limited only to basal zone (i.e., absence of full-thickness dysplasia)
- Based on similar risk to invasive carcinoma, 2-tiered classification advocated
 - Low-grade squamous intraepithelial neoplasia (i.e., mild dysplasia)
 - High-grade squamous intraepithelial neoplasia (i.e., moderate, severe dysplasia/CIS)

ANCILLARY TESTS

- ↑ Ki-67 staining in suprabasal epithelium in higher grade dysplasias
- ↑ p53 immunoreactivity seen in higher grade dysplasias
- p16 not reliable marker in determining extent of UADT dysplasia

Keratinizing Mild Dysplasia




(Left) Keratosis with mild dysplasia shows dysplastic epithelium  that is limited to the basal zone (lower 1/3 of the thickness of the surface epithelium) with only slight elongation of the rete ridges. **(Right)** Keratosis is shown with moderate dysplasia in which the dysplastic epithelium  involves 2/3 of the thickness of the surface epithelium. In addition, the rete ridges are slightly elongated but do not extend downward into the submucosa.



Keratinizing Moderate Dysplasia



Keratinizing Severe Dysplasia

(Left) Keratinizing severe dysplasia shows dysplastic alterations limited to the basal zone , albeit with elongated rete ridges, with surface maturation . **(Right)** Keratinizing severe dysplasia shows markedly elongated rete ridges coupled with dysplastic alterations of most of the epithelium, although surface maturation is present . These findings fall short of classically defined carcinoma in situ (i.e., full-thickness dysplasia), but the findings are tantamount to carcinoma in situ.



Keratinizing Severe Dysplasia



TERMINOLOGY

Abbreviations

- Carcinoma in situ (CIS)

Synonyms

- Keratosis with atypia
- Dysplasia (mild, moderate, severe)
- Squamous intraepithelial lesion or neoplasia
- Laryngeal intraepithelial neoplasia
- Simple hyperplasia
- Basal/parabasal hyperplasia
- Atypical hyperplasia

Definitions

- **Keratinizing dysplasia**
 - Potentially reversible (qualitative) alteration in malignant direction in appearance of epithelial cells with increased likelihood to progress to squamous cell carcinoma
- **CIS**
 - Classically defined as malignant alteration characterized by cellular dysplasia involving entire thickness of the surface epithelium without violation of the basement membrane
 - Considered irreversible process that will progress to invasive carcinoma if left untreated
 - Dysplasia may extend into seromucous glands but is still considered in situ lesion

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Tobacco smoking (most common) and excess alcohol use
 - Alcohol potentiates effect of tobacco smoking
 - Risk of developing dysplastic lesions increases with duration of smoking &/or alcohol use

Infectious Agents

- Role of human papillomavirus (HPV) in development of these lesions remains unproven
 - Prevalence of HPV in premalignant epithelial lesions reported in ~ 12% of cases
 - HPV DNA reported in 12-25% of normal (clinically and histologically) larynges
 - Increasing evidence linking HPV to certain head and neck squamous cell carcinomas
 - Uncertainty remains whether HPV plays any direct role in development of upper aerodigestive tract (UADT) premalignant epithelial dysplasias
 - Limited to no utility of p16 in diagnosis and differential diagnosis of intraepithelial lesions

CLINICAL ISSUES

Epidemiology

- Incidence
 - CIS
 - Represents 1-13% of all laryngeal carcinomas
- Age
 - **Keratinizing dysplasia**
 - Generally limited to adult population with mean age at diagnosis in 6th-7th decades

- **CIS**
 - Wide age range but most common in 7th decade
- Sex
 - Male > female

Site

- **Keratinizing dysplasia**
 - May occur anywhere in larynx but mainly identified along true vocal cord
 - Typically is unilateral but may be bilateral in up to 30% of cases
- **CIS**
 - Can occur anywhere in larynx but most often involves anterior 1/3 of 1 or both true vocal cords
 - May involve entire cord
 - May be bilateral
 - Frequently associated with invasive squamous cell carcinoma either lying adjacent to or remote from one another
 - May exist as isolated lesion unrelated to invasive carcinoma
 - Multifocal areas can occur

Presentation

- Hoarseness or voice changes most common

Natural History

- Risk of progression to invasive carcinoma
 - Circumstantial evidence supports idea that preinvasive dysplasias are potentially reversible following cessation or removal of instigating factor, such as tobacco use
 - Mild and moderate dysplasias felt to be potentially reversible alterations
 - Determining whether mild to moderate dysplasia is reactive or neoplastic is not always achievable
 - Clinically abnormal lesions falling under designation reactive atypias or hyperplastic lesions represent
 - Reversible changes that rarely, if ever, progress to carcinoma
 - Reactive atypias or hyperplastic lesions managed conservatively
 - Problem of predicting malignant potential of dysplastic lesion greatest in moderate dysplasia
 - Impossible to differentiate moderately dysplastic lesions that are reversible from moderate dysplasias representing earliest form of malignant transformation
 - Diagnosis of moderate dysplasia should warrant vigilant patient follow-up
 - Recurrence or persistence may be indicative of malignant transformation
 - Keratotic epithelium without dysplasia carries very low risk of developing invasive carcinoma with reported incidences of 1-5%
 - Keratotic epithelium with dysplasia associated with increased risk for progression or development of premalignant or overtly carcinomatous changes, varying from 11-18%
 - Risk of malignant transformation in keratosis with dysplasia represents increase of 3-5x compared with carcinoma arising in keratotic lesions without dysplasia

- Risk for progression to invasive carcinoma in keratosis with atypia varies depending on degree of atypia/dysplasia
 - Mild dysplasia: ~ 6%
 - Moderate dysplasia: ~ 23%
 - Severe dysplasia: ~ 28%
 - Average latency period from diagnosis of keratosis with atypia to invasive carcinoma is 3.8 years
- No statistical difference in risk to progression to invasive carcinoma in UADT moderate dysplasia and severe dysplasia
 - Based on similar risk to invasive carcinoma, classification akin to Bethesda system used for uterine cervix to include 2 categories for UADT dysplasia
 - Low-grade squamous intraepithelial neoplasia (i.e., mild dysplasia)
 - High-grade squamous intraepithelial neoplasia (i.e., moderate and severe dysplasia)
- Important to note that diagnosis of keratinizing severe dysplasia/CIS
 - Is associated with multifocal lesions, including other foci of keratinizing severe dysplasia &/or invasive carcinoma
 - Frequently occurs adjacent to or near synchronous foci of invasive carcinoma
 - Requires clinical evaluation of entire UADT to exclude possible presence of additional foci of dysplasia or carcinoma
- Wide variation in the literature relative to the incidence of laryngeal carcinoma in situ progressing to invasive carcinoma
 - Discrepant statistics reflect inconsistencies in diagnosis of CIS, which is notoriously subjective diagnosis
 - Collated incidence of laryngeal CIS progressing to invasive carcinoma is 23-27%
 - Latent period of 3-5 years from diagnosis of CIS to invasive carcinoma

Treatment

- Options, risks, complications
 - Cessation of contributing risk factors
 - Mild and moderate dysplasias potentially reversible alterations
 - Circumstantial evidence supports notion that preinvasive dysplasias are potentially reversible following cessation or removal of instigating factor, such as tobacco use
- Surgical approaches
 - **Keratinizing dysplasia**
 - Excisional biopsy by vocal cord stripping or by forceps is treatment of choice
 - **CIS**
 - Treatment is not standardized
 - Includes vocal cord stripping, laser ablation, cordectomy, hemilaryngectomy, radiation, or combination of procedures

Prognosis

- **Keratinizing dysplasia**
 - Excellent cure rates, but recurrent or persistent disease varies from 15-30% following initial therapy

● CIS

- High cure rate (~ 75%), but vigilant follow-up, including periodic laryngoscopic examinations indicated
- Treatment failures result from
 - Extensive &/or multifocal disease
 - Associated undetected invasive squamous carcinoma
 - Extension of CIS to subjacent seromucous glands harboring residual disease following mucosal stripping, which may in turn be nidus for subsequent invasive carcinoma

MACROSCOPIC

General Features

- **Keratinizing dysplasia**
 - Localized, circumscribed flat, or papillary area with white (leukoplakic), red (erythroplakic), or gray appearance
- **CIS**
 - Circumscribed or diffuse lesion with white, red, or gray color and smooth to granular appearance

MICROSCOPIC

Histologic Features

- Histomorphologic changes separated into cellular and maturation abnormalities and include proliferation of immature or "uncommitted" cells
 - Cellular abnormalities
 - Nuclear pleomorphism (i.e., variations in size and shape of nuclei)
 - Nuclear hyperchromasia with irregularities in nuclear contour
 - Increased mitotic activity, especially away from basal zone involving mid and upper (superficial) portions of surface epithelium; may include atypical forms
 - Prominent nucleoli
 - Not unique to dysplasia and may be seen in reactive or reparative process
 - Maturation abnormalities
 - Loss of maturation with increased cellularity in superficial epithelium
 - Normally in mature squamous epithelium, there is decrease in cellularity from basal zone toward keratinizing layers (referred to as maturation)
 - Crowding of cells with loss of polarity
 - Increase in nuclear size relative to cytoplasm (increased nuclear:cytoplasmic ratio)
 - Abnormal keratosis (dyskeratosis)
 - Paradoxical maturation characterized by abnormal keratinization &/or keratin pearl formation in basal zone
 - Dysplastic process begins in basal and parabasal area
- **Grading dysplasia**
 - Mild dysplasia (grade I)
 - Dysplasia limited to lower portions or inner 1/3 of epithelium (basal zone dysplasia)
 - Moderate dysplasia (grade II)
 - Dysplasia involves up to 2/3 of thickness of epithelium
 - Severe dysplasia (grade III)
 - Dysplasia involves from 2/3 to almost complete thickness of epithelium
 - For all intents and purposes, synonymous with CIS

- **Classic or nonkeratinizing dysplasia**
 - Uncommon in UADT, especially in laryngeal glottis and oral cavity
 - Absent surface keratosis
 - Increasing gradations of dysplasia include
 - Mild dysplasia (grade I)
 - Moderate dysplasia (grade II)
 - Severe dysplasia (grade III) representing full-thickness replacement of squamous epithelium by atypical, small, immature basaloid cells and synonymous with CIS
 - Grading scheme is reproducible and clinically useful
- **Keratinizing dysplasia**
 - Most common type of dysplasia in UADT
 - Keratinizing dysplasias include surface keratinization with maturation but cellular (and often architectural) abnormalities
 - Surface maturation retained with only partial replacement of epithelium by dysplastic cells from which invasive carcinoma may develop
 - Similar grading as nonkeratinizing dysplasia (i.e., mild, moderate, and severe) depending on degree and extent of cellular and maturation alterations
 - Criteria for evaluating keratinizing dysplasias are less defined than nonkeratinizing dysplasia, and diagnosis of keratinizing severe dysplasia remains controversial
 - Definition of keratinizing severe dysplasia, especially laryngeal and oral cavity, broader, more heterogeneous, and less reproducible than nonkeratinizing dysplasias
 - Keratinizing dysplastic epithelium often hyperplastic with elongated and irregular-appearing rete ridges extending downward into submucosa
 - Keratinizing severe dysplasia includes epithelial alterations so severe that there would be high probability for progression to invasive carcinoma if left untreated
 - Prior statement, while true, represents major source of subjectivity in evaluating these lesions as well as reason for lack of diagnostic reproducibility
 - Histopathologic interpretation and grading of keratinizing dysplasias of UADT tract are imprecise and subjective
 - Confusion and misunderstandings occur between clinician and pathologist that may result in inappropriate patient management
- **CIS**
 - Dysplastic process involves entire thickness of squamous epithelium without violation of basement membrane
 - Uncommon in UADT and, when identified, typically seen in nonkeratinizing epithelia (e.g., oropharynx, nasopharynx, sinonasal tract)
 - Typically in these locations, rare for CIS alone to be associated with clinically evident lesion &/or to be isolated histologic finding in absence of associated (clinically evident) invasive carcinoma
 - Squamous epithelium may or may not be thickened
 - Alterations include
 - Loss of cellular maturation and polarity
 - Increase in nuclear:cytoplasmic ratio

- Nuclear pleomorphism with hyperchromasia and irregular nuclear contours
- Presence of mitoses in all layers of mucosa, including normal and abnormal forms
- Dyskeratosis may be present
- Extension to mucoserous glands still represents CIS
- Use of CIS as classically defined (i.e., full-thickness dysplasia) in keratinizing dysplasias is inappropriate, as maturation is often present and full-thickness intraepithelial dysplasia is uncommon
 - More appropriate designation is keratinizing severe dysplasia
 - Such lesions capable of progressing to invasive carcinoma in absence of full-thickness epithelial dysplasia ("drop-off" carcinoma)

ANCILLARY TESTS

Immunohistochemistry

- No known reliable markers to assist in diagnosis and differential diagnosis
- Increased proliferation rates in suprabasal epithelium by Ki-67 (MIB-1) staining seen in higher grade dysplasias
- Increased p53 immunoreactivity seen in higher grade dysplasias
- p16 not reliable marker in determining presence or absence of dysplasia in larynx
 - Predominance of keratinizing dysplasia in larynx (often etiologically linked to tobacco and alcohol use) not associated with transcriptionally active virus

DIFFERENTIAL DIAGNOSIS

Reactive Epithelial Changes

- May include keratosis with thickened epithelium and elongated rete ridges but absent dysplastic epithelium
- Discerning reactive from dysplastic cellular changes can be problematic

Transitional Epithelium

- Normal epithelium lying at transition between respiratory-type epithelium of supraglottis and subglottis and squamous epithelium of glottis
- On biopsy, may present diagnostic challenge with dysplastic epithelium
- Characterized by increased cellularity with lack of maturation but absence of nuclear pleomorphism, mitotic activity

Infectious Disease

- Presence of neutrophilic infiltrate along surface &/or within epithelium may indicate presence of fungi
- Special stains for fungi, including PAS &/or Grocott methenamine silver indicated
 - Fungal forms (spores &/or hyphae) limited to superficial aspect of epithelium represent colonization
 - Fungal forms within depth of epithelium represent infestation and require antifungal therapy
 - Fungal infestation may cause clinical and histopathologic lesion simulating squamous epithelial lesion

Classification Schemes for Epithelial Precursor Lesions

WHO Classification*	SIN	Ljubljana Classification	Amended Ljubljana Classification
Mild dysplasia	SIN 1	Basal/parabasal cell hyperplasia	Low-grade SIL
Moderate dysplasia	SIN 2	Atypical hyperplasia	High-grade SIL
Severe dysplasia**	SIN 3	Atypical hyperplasia	High-grade SIL
CIS	SIN 3	CIS	CIS

*CIS = carcinoma in situ; SIN = squamous intraepithelial neoplasia; SIL = squamous intraepithelial lesion. *Recommended classification scheme. **For all intents and purposes, severe dysplasia and CIS represent the same lesion.*

Histomorphologic Changes of Dysplasia

Cellular Abnormalities	Maturation Abnormalities
Nuclear pleomorphism with abnormal variation of nuclear size (anisonucleosis) and cell size (anisocytosis)	Loss of maturation
Nuclear hyperchromasia	Loss of cellular polarity
Increased mitotic activity, especially away from basal zone	Increased nuclear:cytoplasmic ratio
Atypical mitoses	Abnormal keratinosis (dyskeratosis)
Prominent nucleoli	Paradoxical keratinization

In conjunction with cellular and maturation abnormalities, alterations in the architectural appearance, including elongated and irregular-appearing rete pegs, may factor in the determination of the extent of dysplasia.

Upper Aerodigestive Tract Intraepithelial Dysplasia

Proposed 2-Tier Classification

Low-grade squamous intraepithelial lesion encompassing mild dysplasia

High-grade squamous intraepithelial lesion encompassing moderate and severe dysplasia/CIS*

**The risk of progression to invasive carcinoma relative to upper aerodigestive tract moderate dysplasia (~ 23%) and severe dysplasia (~ 28%) is not statistically significant. As such, consideration is being given to group moderate and severe dysplasia under a single category of high-grade squamous intraepithelial neoplasia akin to the Bethesda classification for uterine cervical dysplasias.*

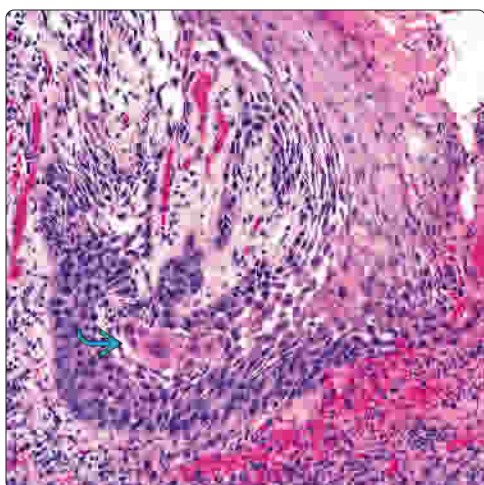
Microinvasive Carcinoma

- Diagnosis reserved for cases showing definitive evidence of violation of surface epithelial basement membrane by malignant cells (nests, individual cells) with at least superficial invasion into submucosa

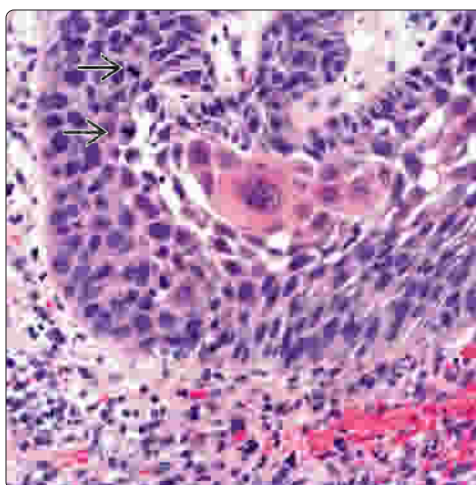
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Paradoxical Maturation

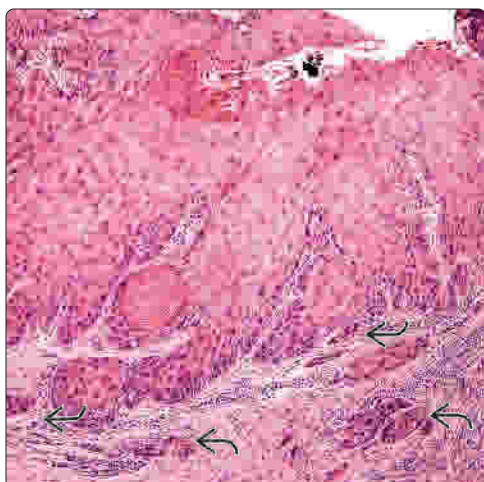


Paradoxical Maturation

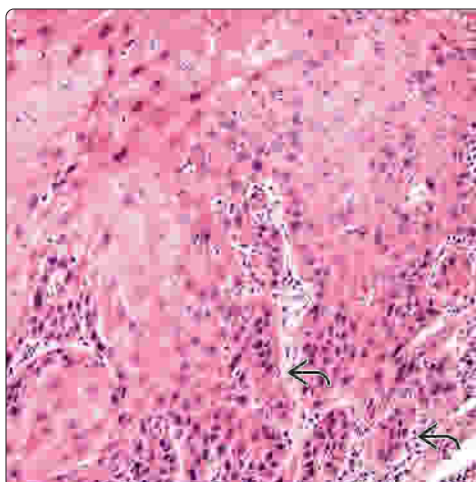


(Left) Although the epithelium is tangentially sectioned, there is paradoxical maturation [box], which is characterized by the presence of abnormal keratinization &/or keratin pearl formation in the basal zone; foci of invasive carcinoma were seen adjacent to this area (not shown). (Right) At higher magnification, the focus of paradoxical maturation includes cells with obvious keratinization located in the lower zone epithelium and present among the dysplastic epithelial cells that include mitotic figures [box].

"Drop-Off" Carcinoma

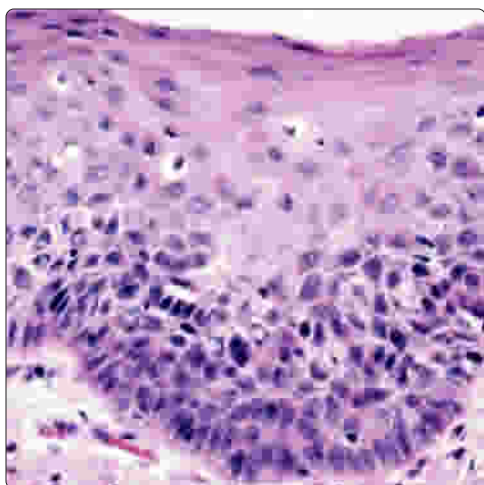


"Drop-Off" Carcinoma

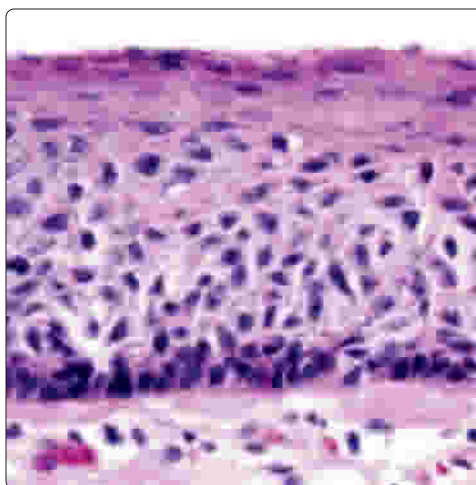


(Left) Invasive squamous carcinoma [box] is seen arising from keratinizing dysplasia in which the dysplasia is limited to the lower zone in the absence of full-thickness intraepithelial dysplasia. Such an occurrence is the reason that the grading of keratinizing severe dysplasia is problematic, lacking reproducibility. (Right) Invasive squamous carcinoma [box] develops from dysplasia limited to the lower 1/3 of the surface epithelium in the absence of full-thickness intraepithelial dysplasia.

Nonkeratinizing Mild Dysplasia




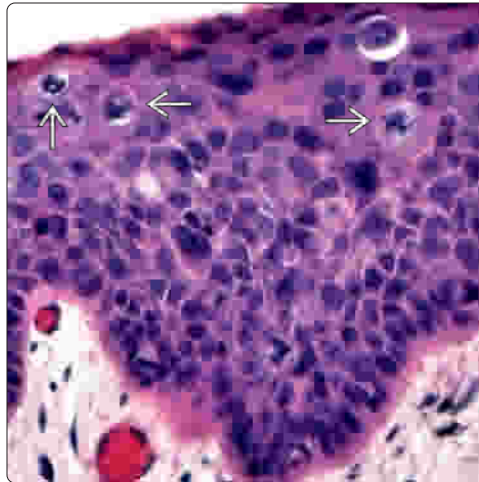
Nonkeratinizing Moderate Dysplasia



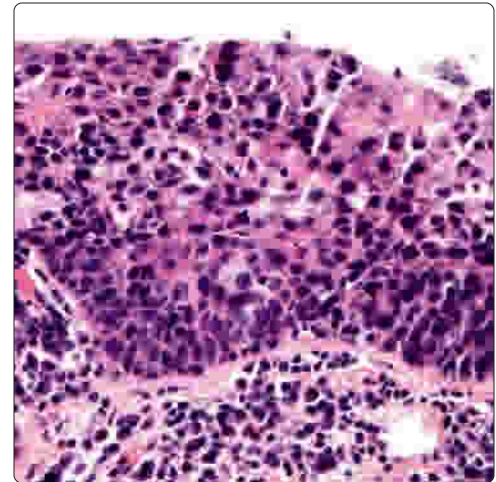
(Left) Laryngeal nonkeratinizing mild dysplasia is characterized by the dysplastic changes limited to the lower 1/3 of the surface epithelium. The grading in nonkeratinizing dysplastic lesions is similar to that of the uterine cervix and is more reproducible than keratinizing dysplasia. (Right) Laryngeal nonkeratinizing moderate dysplasia is characterized by the dysplastic changes involving 2/3 of the surface epithelium.

Nonkeratinizing Severe Dysplasia


(Left) Nonkeratinizing severe dysplasia shows dysplastic changes involving the entire surface epithelium without violation of the basement membrane. Note the numerous mitotic figures , including atypical forms well above the basal zone. These changes are synonymous with carcinoma in situ. (Right) Severe (nonkeratinizing) dysplasia representing classic carcinoma in situ shows full-thickness dysplasia of surface epithelium without invasion beyond the basement membrane.



Nonkeratinizing Severe Dysplasia

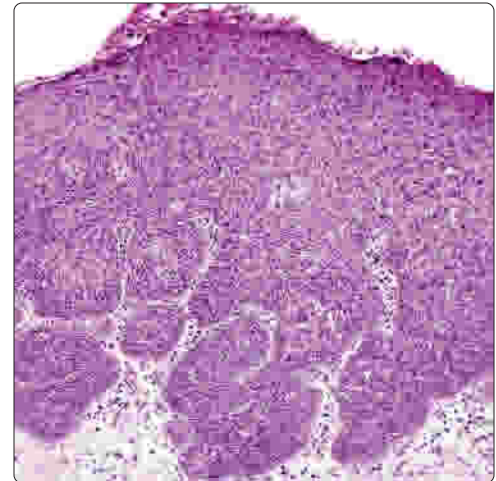


Nonkeratinizing Severe Dysplasia



(Left) Laryngeal nonkeratinizing severe dysplasia is shown with extension of the dysplasia to the seromucous gland , a finding that still constitutes in situ changes and not invasive carcinoma. (Right) Invasive carcinoma developing from nonkeratinizing severe dysplasia conforms to classic carcinoma in situ. Such a finding is much less common than the development of invasive carcinoma from keratinizing dysplasia lacking full-thickness dysplasia of the surface epithelium.

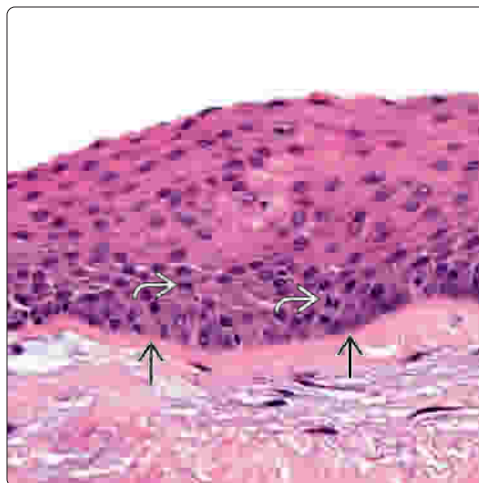


Invasive Carcinoma in Nonkeratinizing Severe Dysplasia

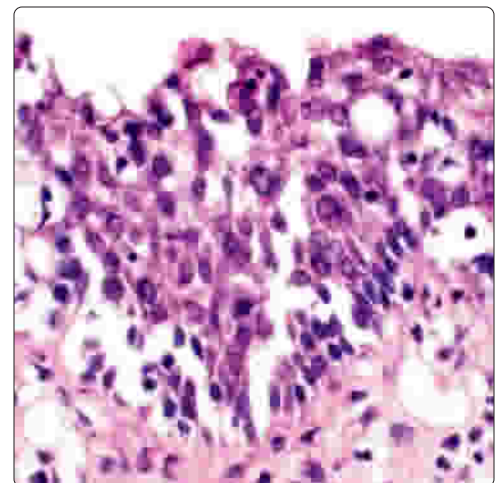


Normal Glottic Epithelium

(Left) Normal true vocal cord shows nonkeratinizing squamous epithelium characterized by cellular maturation. Normally, mitotic figures  can be seen in the basal zone  (proliferation zone). (Right) Transitional-type epithelium predominantly composed of basaloid or immature squamous cells may be misdiagnosed as carcinoma in situ, but cells have vesicular nuclei, smooth nuclear contours, absence of significant pleomorphism, and absence of mitoses away from the basement membrane.



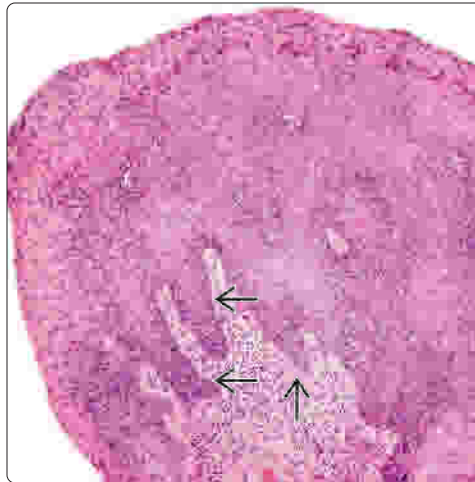
Normal Transitional Zone Epithelium



Keratosis Without Dysplasia

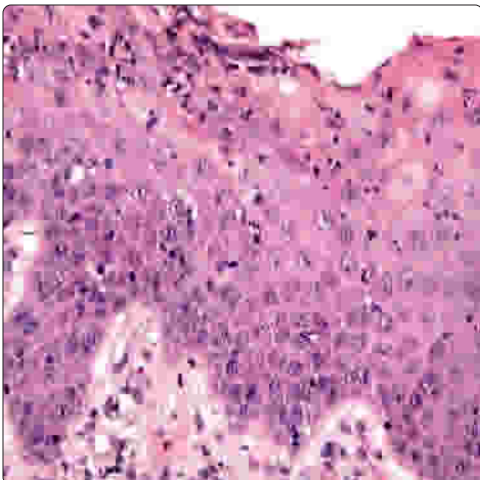


Keratosis Without Dysplasia

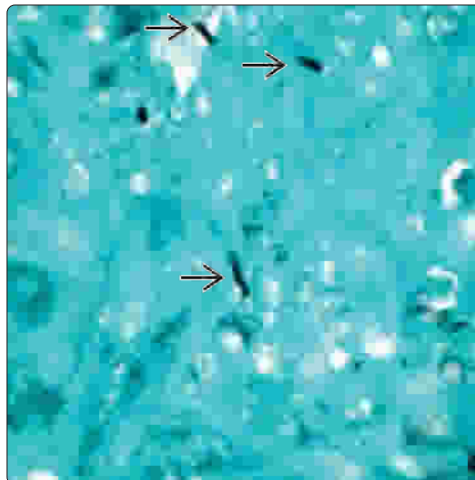


(Left) Abnormal vocal cord epithelium shows surface keratinization [X], epithelial hyperplasia, and elongated rete ridges [X], but absence of dysplasia. Clinically, this was a leukoplakic lesion. (Right) This laryngeal leukoplakic lesion was clinically suspicious for dysplasia/carcinoma. At low magnification, there is a keratotic epithelial proliferation with downward extension of the rete ridges [X], raising concern for a possible diagnosis of keratinizing dysplasia &/or carcinoma.

Keratosis Without Dysplasia

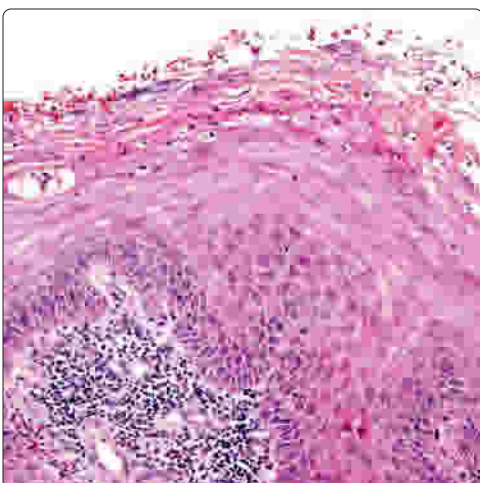


Fungal Infestation

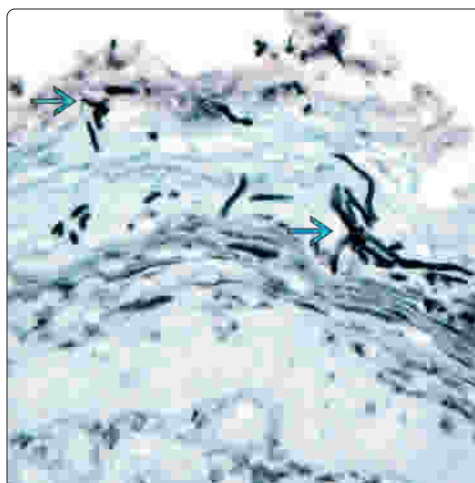


(Left) At higher magnification, there is reactive epithelial atypia but absent dysplasia. Note the neutrophilic infiltrate along the surface epithelium as well as throughout the epithelial layers, raising concern for the presence of fungi. (Right) Histochemical (GMS) staining shows the presence of fungal hyphae [X] within the depth of the epithelium, indicative of fungal infestation, the likely cause of the keratosis and irregular epithelial hyperplasia.

Keratosis Without Dysplasia



Fungal Colonization



(Left) This Laryngeal leukoplakic lesion was clinically suspicious for dysplasia/carcinoma. At low magnification, there is a keratotic epithelial proliferation without dysplasia and a neutrophilic infiltrate limited to the superficial epithelium. (Right) In contrast to fungal infestation, fungal colonization shows the fungal forms [X] limited to the surface &/or superficial aspects of the squamous epithelium, but not in the depths of the surface epithelium.

Conventional Squamous Cell Carcinoma

KEY FACTS

TERMINOLOGY

- Malignant neoplasm characterized by squamous cell differentiation
- Microinvasive carcinoma includes presence of invasive carcinoma extending into stroma no more than 0.5 mm measured from epithelial basement membrane and without angioinvasion

ETIOLOGY/PATHOGENESIS

- Tobacco and alcohol, gastroesophageal reflux

CLINICAL ISSUES

- Laryngeal squamous cell carcinoma (SCC) accounts for ~ 0.8% of all cancers; 1.0% of all cancers in males, ~ 0.3% of all cancers in females
- Represents > 95% of all laryngeal carcinomas
- Represents ~ 90% of all head & neck carcinomas
- Accounts for > 95% of laryngeal malignancies
- Most common in men in 5th-7th decades

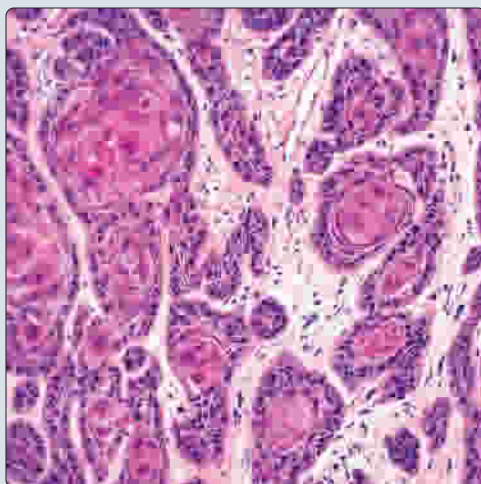
- Glottic carcinomas are most common
 - Majority arise from anterior portion of true vocal cord
 - Hoarseness is earliest symptom
- Various treatment modalities dependent on clinical stage
- Supraglottic cancers account for 30-35% and subglottic carcinomas for < 5% of all laryngeal carcinomas

MICROSCOPIC

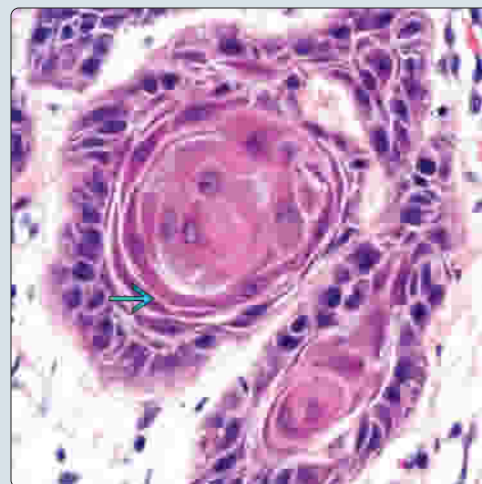
- Histologic categories: In situ or invasive
 - Expansive vs. jagged, single cell infiltration
- Grade: Well-, moderately, or poorly differentiated, based on
 - Disorganized growth, loss of polarity, loss of maturation
 - Increased nuclear to cytoplasmic ratio, hyperchromasia, nuclear chromatin irregularities, dyskeratosis/paradoxical maturation
 - Increased mitoses, atypical mitoses
 - Desmoplastic stroma, inflammatory infiltrate
 - Keratin granuloma supports presence of invasion

Invasive Well-Differentiated SCC

(Left) Well-differentiated squamous cell carcinoma (SCC), as seen here, is characterized by cohesive nests of tumor with associated dysplastic cells infiltrating into the submucosa with associated desmoplasia. **(Right)** At higher magnification, the carcinoma includes cells with prominent keratinization (bright eosinophilic cytoplasm) as well as the presence of intercellular bridges [X]. The more a neoplasm looks like its cell of origin, the better differentiated it is. This SCC is well differentiated.

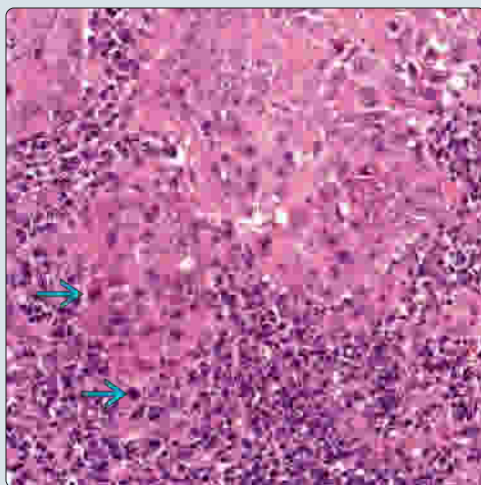


Invasive Well-Differentiated SCC

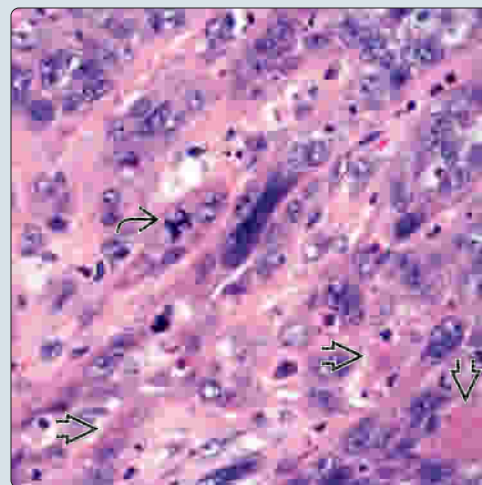


Invasive Moderately Differentiated SCC

(Left) Moderately differentiated SCC characterized by cohesive tumor nests infiltrating the submucosa retains evidence of squamous differentiation in the form of individual cell keratinization, but with greater pleomorphism and mitotic activity [X] than well-differentiated SCC. **(Right)** Invasive poorly differentiated SCC composed of small clusters & individual malignant cells with marked nuclear pleomorphism and an atypical mitotic figure [X] is shown. Cells with keratinization [X] support a diagnosis of SCC.



Invasive Poorly Differentiated SCC



TERMINOLOGY

Abbreviations

- Squamous cell carcinoma (SCC)

Definitions

- Malignant neoplasm characterized by squamous cell differentiation
- Microinvasive carcinoma (superficially invasive SCC)
 - Malignant cells that have penetrated basement membrane and infiltrate into superficial compartment of lamina propria
 - Various definitions, but presence of invasive carcinoma extending into stroma no more than 0.5 mm measured from epithelial basement membrane and without angioinvasion is preferred
 - Can occur in 2 unrelated phases
 - Development from (and as continuum of) carcinoma in situ
 - Typically occurs in setting of nonkeratinizing dysplasia with full thickness intraepithelial dysplasia
 - Not common occurrence relative to dysplastic lesions of larynx (and oral cavity)
 - Development from epithelium demonstrating dysplastic alterations representing severe dysplasia but lacking full thickness intraepithelial dysplasia
 - Typically occurs in setting of keratinizing high-grade dysplasia (i.e., moderate to severe) in which (micro)invasive carcinoma is seen originating from dysplastic epithelial changes limited to basal zone epithelium with remainder of more superficially located epithelium lacking dysplastic change
 - Such invasive carcinomas are referred to as "drop-off" or "drop-down" carcinoma
 - Reinforces fact that in upper aerodigestive tract, particularly in larynx and oral cavity, "classic" carcinoma in situ is not prerequisite for development of (micro)invasive SCC
- Invasive SCC
 - Cytologically malignant tumor nests in submucosa with irregular outlines, infiltrative borders, and associated desmoplasia
 - Presence of keratin granuloma formation in submucosa represents supportive evidence of (at least) microinvasive carcinoma
 - Invasive carcinomas may be extremely well-differentiated with minimal, if any, malignant cytologic features
 - May include lymph-vascular invasion &/or perineural invasion

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Genetic predisposition is uncommon, but immune deficiency and old age play role
 - Lynch II syndrome, Bloom syndrome, Fanconi anemia, xeroderma pigmentosum, ataxia telangiectasia, and Li-Fraumeni syndrome are all associated with SCC

Environmental Exposure

- Association with tobacco smoking
 - Tobacco linked to glottic carcinoma

- > 5% of patients with laryngeal carcinoma occur in nonsmokers

- Alcohol consumption
 - Independent of tobacco, but multiplicative if both are used
 - Alcohol linked to supraglottic carcinoma but less of important risk factor as compared to tobacco use
- Other potential contributing etiologic factors associated with, but not definitively linked, as direct cause of squamous cell carcinoma include
 - Dietary deficiencies (vitamin A, vitamin C, iron)
 - Radiation exposure (therapeutic and environmental)
 - Environmental/occupational exposure (asbestos, nickel, wood, air pollution, isopropyl alcohol, mustard gas, others)
 - Gastroesophageal reflux or laryngopharyngeal reflux (chronic inflammation as mutagen)
- Protective effect by high intake of fruits and vegetables

Infectious Agents

- Human papillomavirus (HPV), HHV-8, Epstein-Barr virus may have minor causative role

Precursor Lesions

- Laryngeal SCC originates from surface squamous epithelium
- Leukoplakia clinically: 50% show no dysplasia histologically
- Epithelium goes through arc of development to invasive carcinoma
 - Reactive/keratosis: 1-5% of patients develop SCC
 - Mild dysplasia: 6% of patients develop SCC
 - Moderate/severe dysplasia/CIS: 28% of patients develop SCC

Multifactorial

- All factors probably interact in multistep process

CLINICAL ISSUES

Epidemiology

- Incidence
 - Laryngeal SCC accounts for ~ 0.8% of all cancers; 1.0% of all cancers in males, ~ 0.3% of all cancers in females
 - Represents > 95% of all laryngeal carcinomas.
 - Represents ~ 90% of all head & neck carcinomas
 - Slightly more common in urban than rural areas
- Age
 - Most commonly occurs in 5th-7th decades of life
 - > 1% occur in patients under 30 years of age
 - Children are rarely affected
- Sex
 - Male > > female (6:1)
 - Has been increase of laryngeal carcinoma in women over last 20 years; likely linked to increased tobacco use in women over time period
- Ethnicity
 - Highest in Europeans, South Americans, and African Americans
 - Lowest in Southeast Asians and Central Africans

Site

- Glottic carcinomas are most common

Conventional Squamous Cell Carcinoma

- Represents from 60-65% of all laryngeal squamous cell carcinomas
 - Majority arise from anterior portion of true vocal cord
- Supraglottic cancers accounts for 30% to 35% of all laryngeal carcinomas
 - In descending order, supraglottic carcinomas involve: Epiglottis (45-55%), > false vocal cords (12-33%), > aryepiglottic folds (8-21%), > ventricles (4-7%), and arytenoids (5-6%)
 - Marginal or epipharyngeal carcinomas represent carcinomas, involving suprahoid epiglottis and aryepiglottic folds and accounting for ~ 20% of cases
- Subglottic carcinomas considered uncommon, accounting for > 5% of all laryngeal carcinomas
- Geographic differences
 - In Europe (France, Spain, Italy, Finland, Netherlands): Supraglottic SCC predominates
 - In USA, England, and Sweden: Glottic SCC predominates
 - In Japan: No differences noted

Presentation

- Glottic SCC
 - Hoarseness is earliest symptom
 - Symptoms develop early in course of disease as result of interference with vocal cord mobility
- Supraglottic SCC
 - Dysphagia, changes in quality of voice, foreign body sensation in throat, neck mass, hemoptysis, odynophagia, and dyspnea
 - Marginal (epipharyngeal) carcinomas tend to remain quiescent for longer periods and present with more advanced disease
- Subglottic SCC
 - Tend to remain clinically quiescent presenting with advanced disease
 - Most common presenting symptoms relate to airway obstruction (dyspnea, stridor) and to vocal cord fixation (voice changes)
 - May necessitate emergency tracheotomy to maintain airway
- Transglottic carcinoma represents carcinoma that crosses ventricles in vertical direction to involve supraglottis and glottis (and often subglottis)
 - Most likely are glottic cancer with supraglottic extension
 - Neck mass (lymph nodes) more common in transglottic carcinomas
- Tracheal SCC
 - Most common malignant neoplasm of trachea
 - Clinical presentation includes stridor, cough, hemoptysis, hoarseness, weight loss; superior vena cava syndrome may occur in minority of cases
 - Delays in diagnosis common, as symptoms may be attributed to asthma
 - Tracheal carcinoma at level of thyroid can be misinterpreted as invasive thyroid cancer
 - In order of frequency, tracheal carcinomas occur: Lower 1/3 (45%), > upper 1/3 (32%), > middle 1/3 (15%), and > multiple sites (8%)
 - Etiology: Most patients reported to be heavy tobacco smokers

Treatment

- Options, risks, complications
 - Treatment goals include cure, voice sparing (preservation), optimal swallowing, and minimal xerostomia
 - Larynx functions include phonation, respiration, deglutition, and air humidification, and contributes to taste and smell
 - Clinical stage and site play important role in patient management
 - Important factors: Pathologic diagnosis, local tumor extent, regional lymph node status, and distant metastasis
 - Stomal recurrence is infrequent complication (subglottic and postcricoid tumors)
 - Treatment options include surgery &/or radiation
- Surgical approaches
 - Microinvasive carcinoma
 - No standardized approach to treatment
 - Most authorities advocate conservative management with endoscopic removal of lesion (mucosal stripping ± laser ablation) and close clinical follow-up of patient rather than surgical resection (e.g., some type of laryngectomy) or radiation
 - Behavior is similar to that of carcinoma in situ, and if presence of coexisting invasive squamous cell carcinoma can be excluded, then therapy is similar to carcinoma in situ
 - Glottic microinvasive cancers are generally not associated with metastatic disease due to fact that glottic portion of larynx has quantitatively less lymphovascular spaces as compared to supra- and subglottis
 - In contrast to laryngeal glottis, supraglottic microinvasive carcinomas are associated with metastatic disease in ~ 20% of patients
 - Surgical removal of tumor
 - Transoral laser microsurgery, vocal cord stripping, limited resection, open partial laryngectomy, total laryngectomy, &/or neck dissection
 - Movement toward noninvasive, nondestructive management
 - Glottic SCC treatment is dependent on staging
 - For early glottic cancers (T1 and T2) excellent control can be achieved by radiation or partial laryngectomy, or even endoscopic resection in some lesions
 - For advanced glottic cancers (T3 and T4) total laryngectomy ± radiation therapy
 - Supraglottic SCC treatment is dependent on stage
 - For early stage lesions (T1N0 and T2N0) radiation therapy or supraglottic laryngectomy ± adjuvant radiotherapy
 - Advance stage lesions (T3 and T4) combined modalities, often including total laryngectomy and adjuvant radiotherapy
 - Subglottic SCC treatment is dependent on staging
 - For early stage subglottic cancers (T1 and T2) radiotherapy alone or conservative surgery
 - For advanced stage subglottic cancers (T3 and T4) radical surgical extirpation through wide field laryngectomy

- In general, subglottic tumors present with advanced disease and because of proximity to cricothyroid space and cricoid cartilage, surgical treatment usually necessitates total laryngectomy
- Due to involvement of thyroid gland in ~ 10-20% of cases, recommended that 1 or both thyroid lobes be removed
- Tracheal SCC: Surgical resection and primary reconstruction is best curative treatment modality available at present
 - Many tracheal carcinomas are too large or extensive at presentation for surgical cure
 - In patients with advanced disease (i.e., inoperable tumors), radiotherapy can represent management option with variable success in controlling disease

Prognosis

- TNM classification (site, size, and stage) correlates most closely and significantly with disease-free status and overall survival
 - Glottic SCC: 5-year survival rates include
 - T1: 82-96%
 - T2: 51-85%
 - T3: 48-59%
 - T4: 0-30%
 - Supraglottic SCC: 65-75% 5-year survival rate
 - Subglottic SCC: 40% 5-year survival rate
 - Distant metastases occurs in 15-20%; most often to lungs and bones
 - Death in subglottic carcinoma often due to local or stomal recurrence characterized by diffuse infiltration of carcinoma at junction of amputated trachea and skin
 - Dreaded complication of total laryngectomy
 - Tracheal SCC: 50% 5-year survival rate
 - 5-year survival rates 5-15%; 10-year survival rates 6-7%
 - ~ 35% have nodal metastasis at presentation
 - Distant metastases commonly occurs: Primarily to lungs, liver, and bones
- Factors impacting on prognosis
 - Tumor location
 - Transglottic tumors have higher incidence of lymph node metastasis compared with supraglottic and subglottic carcinomas
 - Tumor size
 - Larger tumors have greater chance of metastasis
 - Cervical lymph node metastasis
 - Regional lymph node metastases are relatively common
 - Metastatic tumor to cervical lymph nodes decreases survival by 50%
 - Tumor extending beyond confines of lymph node into perinodal soft tissues is referred to as extranodal extension, which
 - Represents important finding relating to recurrent disease in neck and increased risk for distant metastasis; both associated with decreased survival
 - Presence or absence of extranodal extension should be specifically commented on in pathology report

- Hematogenous metastases are uncommon, usually late in disease
 - Distant spread: Lung followed by liver and bone
- Multiple malignancies
 - Up to 12% of patients with laryngeal carcinoma will develop secondary primary malignant tumor either in lung, another upper aerodigestive tract site or, less commonly, in distant unrelated site
- Tumor histology
 - Poorer differentiation (grade) more likely to disseminate
- Lymph-vascular invasion
 - Vessel invasion associated with increased lymph node &/or distant metastases
 - Associated with recurrence and poor survival
- Perineural invasion
 - Intra- and perineural invasion associated with increased local recurrence and regional lymph node metastases
 - Associated with decreased survival
- Proliferation fraction
 - Higher proliferation index (MIB-1/Ki-67) strongly correlates with poorly differentiated tumors and lymph node metastases
 - It is not independent prognostic factor
- Additional prognostic factors include age, comorbidity (concurrent diseases), and performance status
- Prognostic markers
 - Epidermal growth factor receptor (*EGFR*) and cyclin-D1 overexpression associated with worse clinical outcome
 - *EGFR* status is only useful for patients treated by induction chemotherapy followed by exclusive radiotherapy and not with laryngectomy
 - *CCND1* amplification is associated with poor prognosis
 - Simultaneous *CDK4* and *CCND1* overexpression is associated with poor prognosis
 - *CDKN2A* mutations are associated with poor prognosis (in advanced tumors)

MACROSCOPIC

General Features

- Glottic tumors: Tend to be smaller (have earlier clinical presentation)
- Supraglottic and subglottic tumors: Reach larger size before clinical presentation
- Varying appearances, including white, red, and mixed; flat, polypoid, exophytic, verrucous or endophytic, and ulcerated
- Minute mucosal thickening to large mass filling lumen

MICROSCOPIC

Histologic Features

- Invasive carcinomas varying from well- to poorly differentiated squamous cell carcinomas
 - Glottic carcinomas tend to be moderately to well differentiated
 - Supra- and subglottic carcinomas tend to be moderately to poorly differentiated
 - Presence of anaplasia, mitotic activity, and necrosis is dependent on histologic grade

Conventional Squamous Cell Carcinoma

- Most cancers have evidence of squamous differentiation in form of keratinization and intercellular bridges
 - Keratinizing SCC much more common than nonkeratinizing SCC
- In all locations in situ carcinoma component can be seen adjacent to invasive carcinoma &/or giving rise to invasive carcinoma
- Invasion manifested by
 - Extension through and disruption of basement membrane
 - May be superficial or more deeply infiltrative
 - Presence of solid nests/islands and irregular cords with defined margins or individual/single cell infiltration with poorly defined margin
 - Invasive pattern can be pushing
 - Invasion often associated with desmoplastic stroma that include deposition of extracellular matrix and proliferation of fibroblasts
 - Perineural &/or lymph-vascular invasion
 - Invasion through laryngeal cartilage
 - Often occurs in cartilage that has undergone ossification; latter usually occurs in 3rd decade (and not before)
 - Perichondrium appears to resist invasion and remains intact even when cancer infiltrates and expands cartilage
 - Reason cited for presence of invasion in ossified cartilage includes absence of perichondrium in these areas
 - Cartilaginous invasion usually is found in associated with transglottic cancers
 - Keratin granuloma formation in submucosa represents supportive evidence of (at least) microinvasive carcinoma
 - Represents foreign body reaction to keratin in submucosa
 - Appears as relatively well-formed granuloma formation, including presence of histiocytes and multinucleated giant cells
 - Keratin material may or may not be identified by light microscopy, but may require cytokeratin immunostaining to confirm presence of keratin positive material
 - In absence of cytokeratin positive material, diagnosis of keratin granuloma cannot be rendered
 - Histiocytes and giant cells are CD68 (KP1) positive
- May spread directly to contiguous structures
 - Supraglottic: Piriform sinus, vallecula, base of tongue, preepiglottic space (associated with increased incidence of nodal metastasis)
 - Glottic: Opposite true vocal cord, supraglottis and subglottis, thyroid cartilage, and neck soft tissue
 - Subglottic: Thyroid gland, glottis, supraglottis, hypopharynx, cervical esophagus, and tracheal wall
 - Transglottic: Crosses ventricles, involving supraglottis and glottis

Margins

- Margin status affects recurrence and patient outcome
- Must always be documented in surgical pathology report

DIFFERENTIAL DIAGNOSIS

Pseudoepitheliomatous Hyperplasia (PEH)

- Benign reactive proliferation of elongated, rounded, bulbous epithelial projections, associated with infections and granular cell tumor
- Cellular atypia or nuclear pleomorphism is absent

Necrotizing Sialometaplasia

- Lobular architecture of minor salivary glands maintained, in contrast to effacement in SCC

Squamous Papilloma

- Bland cytomorphology generally devoid of malignant cells, no invasion

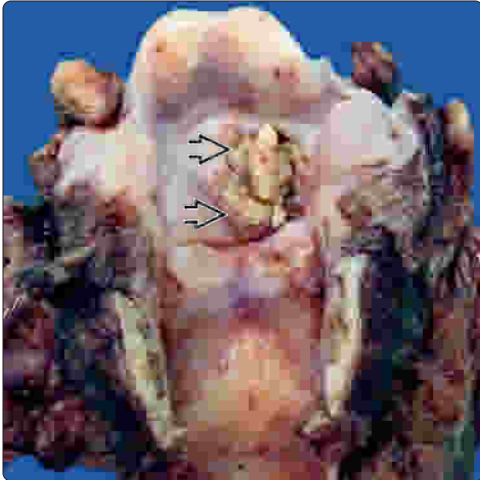
Radiation Changes

- Epithelial, endothelial, and stromal cells affected with specific alterations per cell type

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Supraglottic Squamous Cell Carcinoma

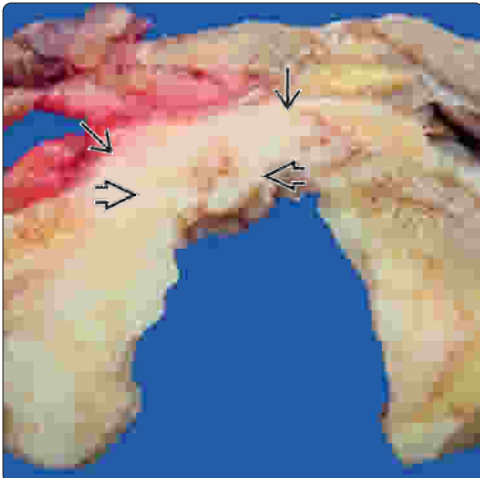


Transglottic Squamous Cell Carcinoma

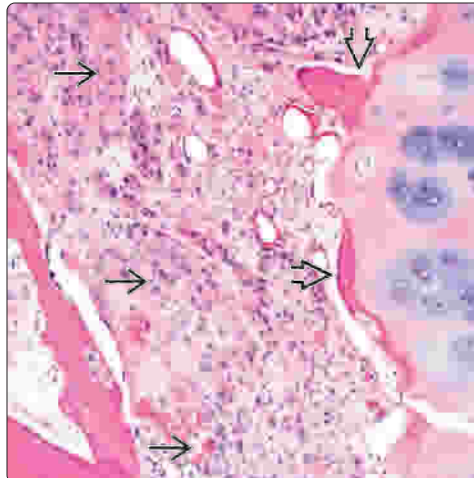


(Left) The SCC seen here is within the supraglottis. The tumor is exophytic, although showing multiple projections of tissue into the laryngeal lumen. There is no involvement of the true vocal cord. (Courtesy J.C. Fowler, MPAS, PA-C.) (Right) This laryngectomy specimen demonstrates a transglottic tumor. The exophytic tumor originated in the glottis with extension to involve the supraglottis and subglottis. The specimen has been opened in the midline posteriorly. (Courtesy J.C. Fowler, MPAS, PA-C.)

Glottic Squamous Cell Carcinoma



SCC Invading Ossified Cartilage

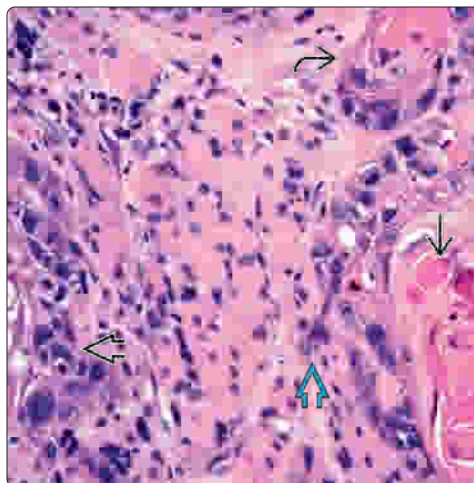


(Left) A cross section through a laryngectomy specimen demonstrates a glottic carcinoma that appears white and was firm to palpation. The carcinoma invaded into and destroyed the cartilage. (Courtesy J.C. Fowler, MPAS, PA-C.) (Right) The histologic features corresponding to the adjacent gross image shows the presence of SCC invading into and through bone. Note the presence of ossified cartilage, a finding that allows for greater permeation of the cartilage by SCC.

Subglottic Squamous Cell Carcinoma



Skeletal Muscle Invasion

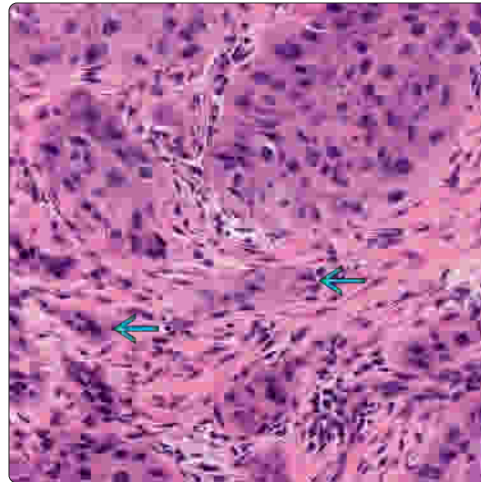


(Left) This tumor only involves the subglottic space. Subglottic SCC is the least common of the laryngeal carcinomas. The tumor has an irregular border, is ulcerated, and was extensively invasive with extralaryngeal extension. (Courtesy J.C. Fowler, MPAS, PA-C.) (Right) Seen here is subglottic SCC varying from well-differentiated to moderately differentiated to poorly differentiated that invaded into the neck and included the involvement of skeletal muscle.

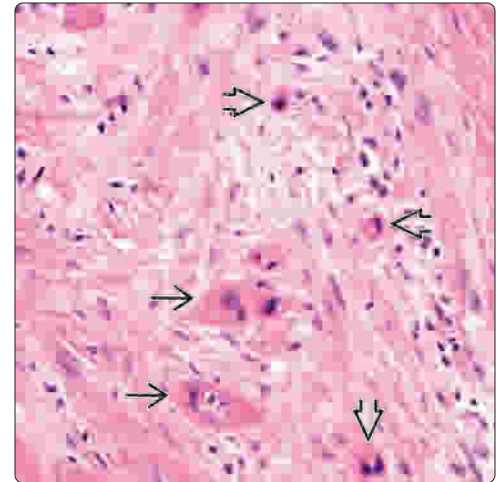
Conventional Squamous Cell Carcinoma

Invasive Squamous Cell Carcinoma

(Left) Invasive moderately differentiated squamous cell carcinoma with associated desmoplastic stroma characterized by collagenized stroma with associated fibroblasts is shown. The invasive tumor includes solid (cohesive) tumor nests with rounded to irregular outlines. (Right) Invasive poorly-differentiated SCC characterized by irregular appearing tumor nests, as well as individual cells with associated desmoplastic stroma, is seen here.

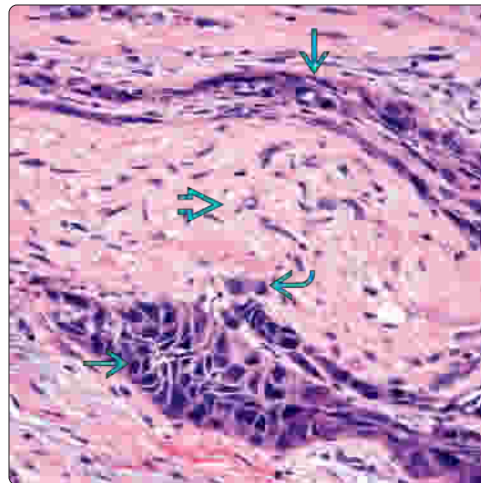


Invasive Squamous Cell Carcinoma

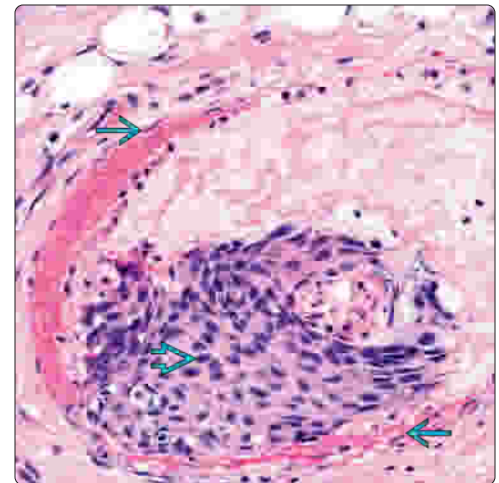


Perineural Invasion

(Left) Seen here is invasive SCC with perineural invasion (neurotropism). The SCC includes cohesive nests located on either side of the nerve that are firmly adherent to the nerve with focal extension into the nerve. (Right) Squamous cell carcinoma with lymph-vascular invasion (LVI) characterized by carcinoma within an endothelial-lined space adherent to the wall of the vessel with associated fibrin thrombus formation.

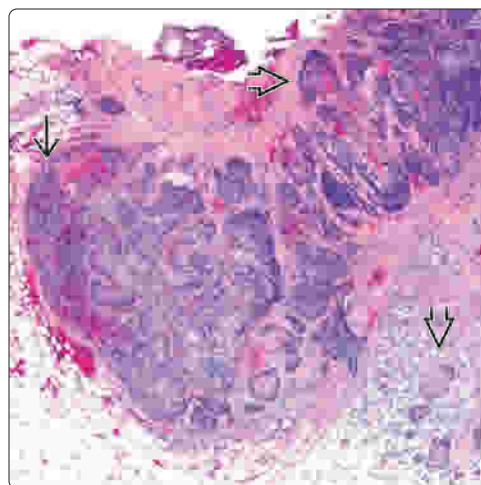


Lymph-Vascular Invasion

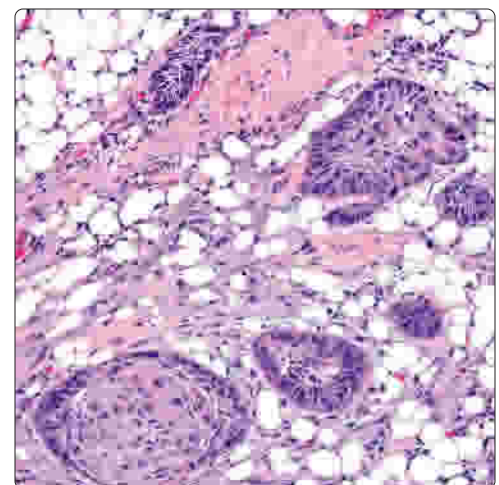


Nodal Metastasis With Extranodal Extension

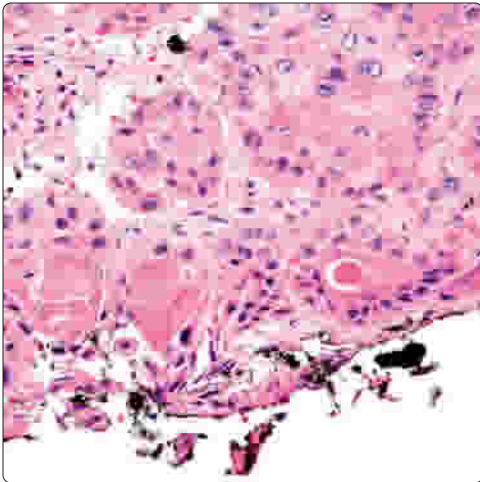
(Left) This is metastatic SCC to the cervical neck lymph node, which is a rather common occurrence. Residual nodal parenchyma is present, but most of the nodal architecture is effaced by the carcinoma that extends into perinodal soft tissue. (Right) Higher magnification shows a rather well-differentiated SCC within perinodal fat. The presence of extranodal extension adversely affects prognosis relating to recurrent disease in the neck and increases the risk for distant metastasis, which are both associated with decreased survival.



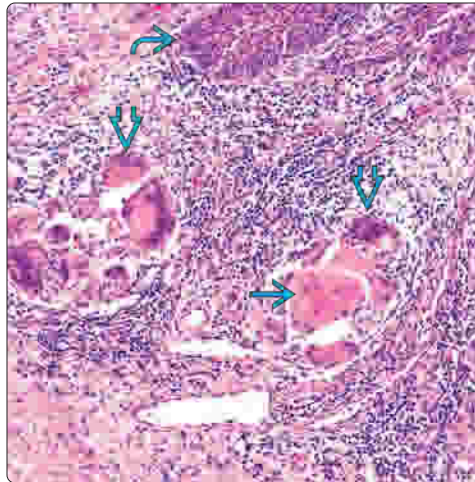
Nodal Metastasis With Extranodal Extension



Invasive SCC at Margin of Resection

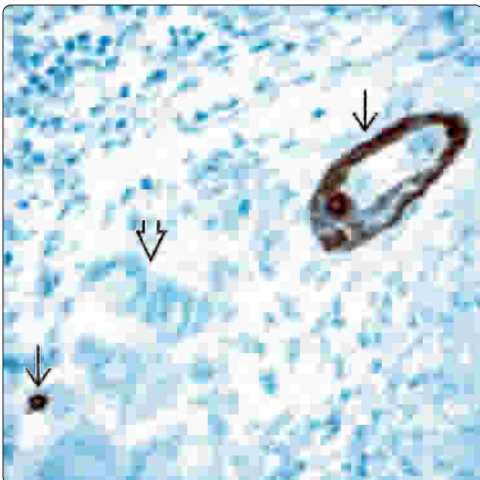


Keratin Granuloma

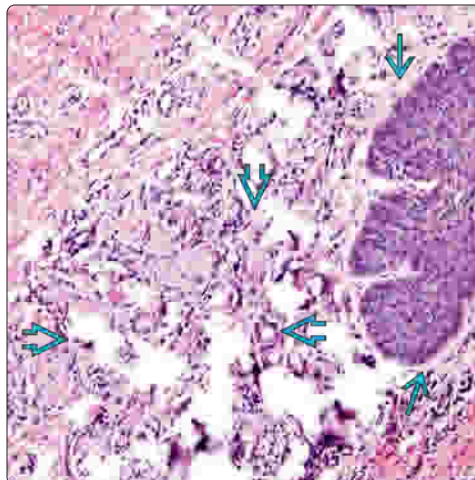


(Left) Excisional biopsy shows a well-differentiated SCC extending to and involving the inked edge of the tissue specimen; indicative of an incompletely excised tumor. (Right) Keratin granuloma, represents a foreign body reaction to keratin in the submucosa, appears as well-formed granuloma formation including the presence of multinucleated giant cells. Carcinoma in situ is present. Submucosal keratin granuloma formation represents supportive evidence of microinvasive carcinoma.

Keratin Granuloma

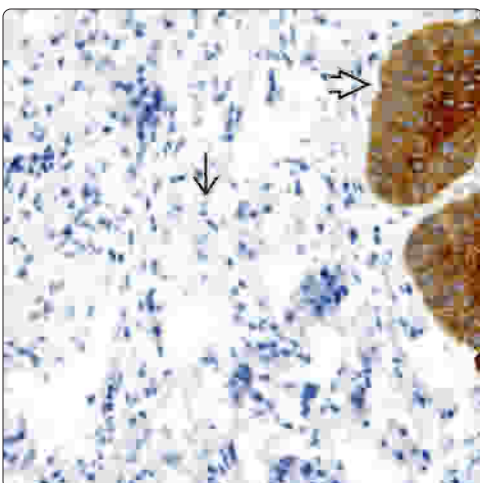


Carcinoma In Situ and Submucosal Granuloma Formation

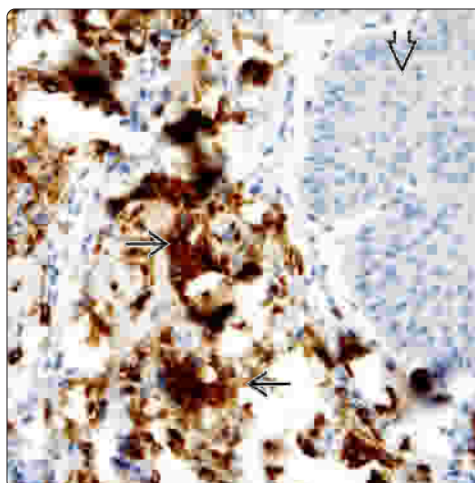


(Left) Cytokeratin staining highlights keratin positive material, confirming a keratin granuloma supportive of invasive carcinoma. The multinucleated giant cells are cytochrome negative. (Right) Another example of carcinoma in situ, as well as the presence of granuloma formation within the submucosa, is suggestive of keratin granuloma and a possible diagnosis of invasive carcinoma. Immunohistochemical staining is needed to evaluate for the presence of keratin.

Keratin-Negative Submucosal Granuloma



Keratin-Negative Submucosal Granuloma



(Left) In contrast to keratin granuloma, cytokeratin staining is absent in the submucosal granuloma. Keratin reactivity is positive in the focus of carcinoma in situ. (Right) CD68 reactivity, a marker of histiocytes, is positive in the giant cells and histiocytes of the submucosal granuloma seen here, while carcinoma in situ is negative. The absence of keratin staining precludes the presence of keratin granuloma and a diagnosis of invasive carcinoma.

Verrucous Carcinoma

KEY FACTS

TERMINOLOGY

- Highly differentiated variant of squamous cell carcinoma with locally destructive but not metastatic capabilities characterized by exophytic &/or warty appearance, absence of epithelial dysplasia, and presence of pushing margins

ETIOLOGY/PATHOGENESIS

- Strong association with tobacco and alcohol abuse
- Most recent data does not support etiologic link to human papillomavirus (HPV), high risk or low risk

CLINICAL ISSUES

- Can occur anywhere in upper aerodigestive tract but most common sites of occurrence include oral cavity (56%) > larynx (35%)
- Most common site of occurrence in larynx is glottic area (anterior true vocal cord)
- Surgery preferred diagnostic modality for all sites
- Prognosis is excellent following complete surgical removal

MACROSCOPIC

- Warty, exophytic, papillary or fungating tumor
- Biopsy large enough to include deep margin and sufficient amount to make accurate diagnosis

MICROSCOPIC

- Multiple filiform, finger-like projections of well-differentiated squamous epithelium, maturing to surface
- Abundant keratosis (ortho- and parakeratosis), "church spire" keratosis, with parakeratotic crypting
- Broad pushing border of infiltration with dense inflammatory response

TOP DIFFERENTIAL DIAGNOSES

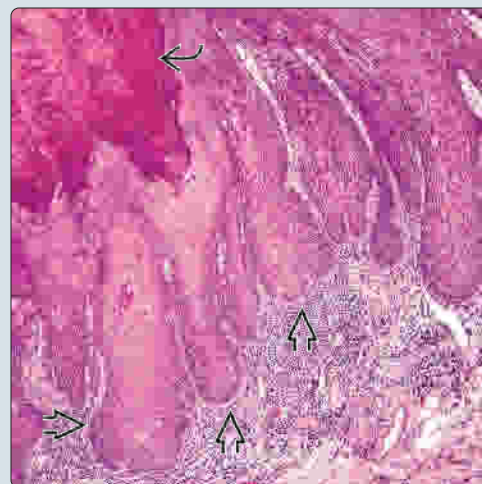
- Proliferative verrucous hyperplasia
- Exophytic/papillary squamous cell carcinoma
- Squamous papilloma
- Pseudoepitheliomatous Hyperplasia
- Verrucous Hyperplasia

Laryngeal Verrucous Carcinoma

(Left) Exophytic/papillary (warty) appearing squamous cell lesion is characterized by keratosis and the presence of a broad, pushing border of infiltration by thickened, bulbous coalescing rete ridges. An inflammatory infiltrate is present at the sharply defined stroma-epithelial interface. **(Right)** Prominent (tiered) keratotic squamous epithelial lesion is shown in which the elongated and broad appearing rete ridges extend downward into the submucosa.

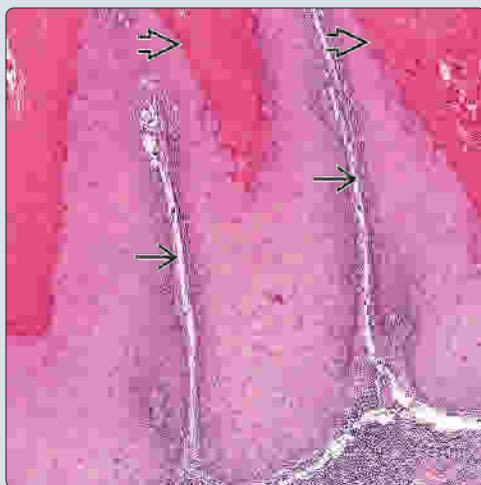


Laryngeal Verrucous Carcinoma



Laryngeal Verrucous Carcinoma

(Left) Broad rete ridges composed of squamous epithelium show maturation toward the surface. There is prominent keratinization with parakeratosis and the presence of delicate fibrovascular cores. **(Right)** Verrucous carcinoma (VC) is comprised of a bland, nonmitotically active-appearing, maturing squamous epithelium. The absence of dysplasia creates problems in differentiating VC from epithelial hyperplasia, especially in biopsy material.



Laryngeal Verrucous Carcinoma



TERMINOLOGY

Abbreviations

- Verrucous carcinoma (VC)

Synonyms

- Ackerman tumor

Definitions

- Highly differentiated variant of squamous cell carcinoma with locally destructive but not metastatic capabilities characterized by exophytic &/or warty appearance, absence of epithelial dysplasia, and presence of pushing margins

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Strong association with tobacco and alcohol abuse

Infectious Agents

- Most recent data does not support etiologic link to human papillomavirus (HPV), high risk or low risk
 - Active role of HPV is more likely as promoter in multistep process of carcinogenesis in squamous cells of upper aerodigestive tract
 - 2 viral oncoproteins of high risk HPVs, E6 and E7, promote tumor progression by inactivating the p53 and retinoblastoma tumor suppressor gene products, respectively, thereby disrupting cell-cycle regulatory pathways in genetic progression to H&N squamous cell carcinoma

CLINICAL ISSUES

Epidemiology

- Age
 - Mean: 6th and 7th decades
- Sex
 - Male > female (4:1)
 - In oral cavity, female > male (3:2)

Site

- Can occur anywhere in upper aerodigestive tract but most common sites of occurrence include oral cavity (56%) > larynx (35%)
- Larynx is 2nd most common site of occurrence
 - Accounts for 15-35% of all VCs
 - Represents from 1-4% of all laryngeal carcinomas
 - Most common site of occurrence in larynx is glottic area (anterior true vocal cord)
 - Less common sites of occurrence include supraglottis, hypopharynx and subglottis, and trachea

Presentation

- Hoarseness is most common symptom
 - Other symptoms include airway obstruction, weight loss, dysphagia, and throat pain
- Enlarged lymph nodes are common, but they are reactive rather than neoplastic

Treatment

- Surgical approaches
 - Surgery preferred diagnostic modality for all sites
 - In larynx, extent of surgery depends on clinical stage

- T1: Laser excision; T2: Hemilaryngectomy; T3, T4: Total laryngectomy

- Radiotherapy can be used in selected cases
 - May be used in patients with advanced disease &/or in patients who are not good surgical candidates
 - Previous reason cited for not irradiating VC is purported induction of anaplastic transformation following radiotherapy
 - Reported VCs treated by radiation that underwent anaplastic transformation most likely did not represent VCs but represented hybrid carcinomas or pure conventional SCC misdiagnosed as VC

Prognosis

- Excellent following complete surgical removal
 - Overall 5-year survival: 85-95%
 - Survival lower with radiation only (65%)
- Local recurrence may occur if incompletely excised
- Cervical adenopathy may be associated with VC representing reactive changes and not metastatic disease
 - Neck dissection generally not warranted in treatment
- Distant metastases do not occur
- Death due occurs in ~ 4% of cases, resulting from local uncontrollable disease
- Hybrid carcinomas have potential to metastasize
 - Hybrid carcinomas should be staged and managed as conventional squamous cell carcinomas

MACROSCOPIC

General Features

- Tan or white, warty, fungating or exophytic, firm to hard mass
- In general, tumors are attached by broad base

Size

- Variable; measuring up to 9-10 cm in diameter

MICROSCOPIC

Histologic Features

- Highly differentiated type of SCC
- Squamous epithelium lacks cytologic criteria of malignancy
 - Very well-differentiated squamous epithelium
 - Cells are typically larger than those seen in conventional SCC
 - Maturation toward surface
 - If dysplasia present, it is focal and limited to basal zone
- Surface contains papillary fronds
 - Multiple filiform, finger-like projections of well-differentiated squamous epithelium
 - Thickened, club-shaped papillae with thin fibrovascular cores
 - Papillae may show surface ulceration
- Abundant keratosis (ortho- and parakeratosis)
 - Thick, keratinized layer covering epithelium
 - "Church spire" keratosis
 - Parakeratotic crypting (collections of parakeratotic cells with debris)
 - Intraepithelial microabscesses can be identified
 - Extravasated keratin may elicit foreign body giant-cell stromal reaction

- Broad pushing border of infiltration
 - Blunt, intrastromal invaginated folds
 - Bulbous coalescing rete ridges
 - Downward dipping of epithelium creates "cup" or "arms" around periphery
 - This interface is excellent location for biopsy
 - Extends below level of identifiable intact subjacent normal epithelium
 - Associated with dense lymphoplasmacytic inflammatory response
- Limited mitotic figures, if present at all
 - Limited to basal zone if found, and not atypical
- Chronic inflammatory cell infiltrate composed of lymphocytes, plasma cells, and histiocytes may be prominent advancing from tumor
- **Hybrid carcinoma**
 - Tumor showing mixed histology including foci of VC and foci of conventional squamous cell carcinoma
 - Biologic risk is that of conventional SCC including potential for metastatic tumor
 - May occur in larynx but more commonly seen in oral cavity lesions
 - Careful sampling and evaluation of depth of lesion is important to exclude possible diagnosis of hybrid carcinoma
- **Biopsy diagnosis of VC**
 - Pathologic diagnosis of VC may be extremely difficult requiring multiple biopsies over several years
 - Adequate biopsy material is critical to interpretation and should include good epithelial-stromal interface
 - Pathologist should not over interpret verrucoid lesion as carcinoma without adequate tissue sampling including presence of ample subjacent stroma
 - diagnosis of VC at initial presentation and biopsy extremely challenging given overall bland cytomorphology and shared features with reactive verrucoid hyperplastic lesions
 - Diagnosis of VC at initial presentation and biopsy extremely challenging given overall bland cytomorphology and shared features with reactive verrucoid hyperplastic lesions
 - Recurrence of tumor at future time may be clue to diagnosis of VC
- Rare aggressive form of oral leukoplakia with tendency to recur, often with multifocal oral involvement, and to undergo malignant transformation
- Clinical and pathologic appearance in the early stages of PVL no different than any other type of leukoplakic lesion making diagnosis of PVL in its early stages virtually impossible
- Histologically composed of hyperplastic squamous epithelium with regularly spaced, verrucous epithelial projections and associated hyperkeratosis
 - Sharply defined lesion and in contrast to downward growth into underlying submucosal compartment by bulbous rete pegs in VC, hyperplastic epithelium in PVL remains superficial (without submucosal invasion) and does not extend deeper than that of adjacent epithelium

Verrucous Hyperplasia

- One of most difficult and problematic lesions to diagnose and differentiate from VC
- Hyperplastic squamous epithelium, regularly spaced, verrucous projections, hyperkeratosis, sharply defined stromal interface
- Complete excision and close patient follow-up recommended to exclude recurrence or progression
 - In presence of recurrent lesion months to years later diagnosis of VC is likely

Exophytic/Papillary Squamous Cell Carcinoma

- High-grade intraepithelial dysplasia/carcinoma in situ and invasive growth

Squamous Papilloma

- Thin, well-formed papillary fronds, limited keratinization, and usually presence of koilocytotic atypia

Pseudoepitheliomatous Hyperplasia

- Nonatypical inverted epithelial proliferation, with bulbous rete extensions into stroma
- Lacks exophytic/papillary growth, and usually is not large lesion clinically
- May be associated with infection or granular cell tumor

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ANCILLARY TESTS

Immunohistochemistry

- p53 overexpression can be seen (~ 40%)

PCR

- HPV types 6, 11, 16, and 18 are variably detected

DIFFERENTIAL DIAGNOSIS

Proliferative Verrucous Leukoplakia

- Proliferative verrucous leukoplakia (PVL) represents interrelated and irreversible mucosal lesion of oral cavity and upper aerodigestive tract with propensity to progress to either VC or conventional types of squamous cell carcinoma
- Considered premalignant lesion

Oral Cavity Biopsy

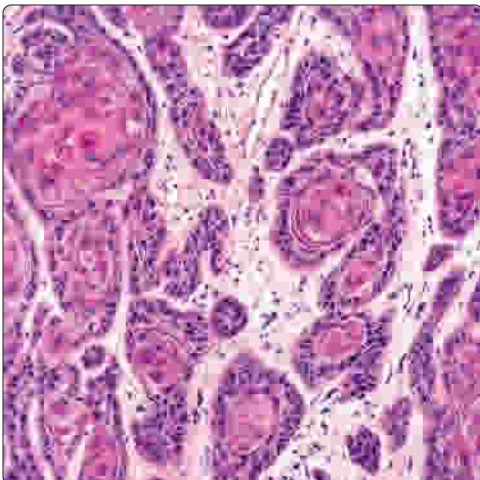


Oral Cavity Biopsy

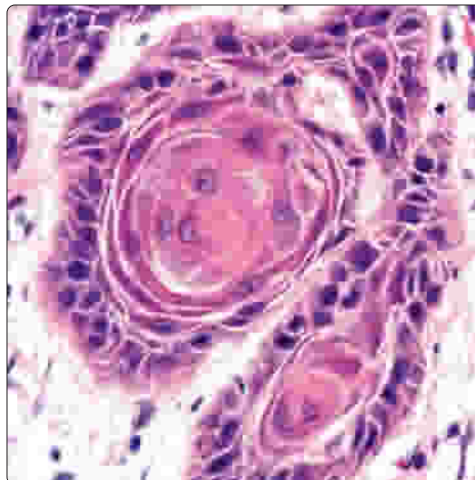


(Left) At low magnification, an exophytic, warty-appearing squamous epithelial proliferation is seen with elongated and downwardly extending rete ridges, but limited to absent submucosa is present. (Right) The squamous epithelium lacks evidence of intraepithelial dysplasia. Along the depth of the lesion there is minimal to absent submucosa. Based on the biopsy, especially if this is the initial presentation, a diagnosis of VC cannot be confirmed or differentiated from a benign epithelial proliferation.

Oral Cavity Hybrid Carcinoma



Oral Cavity Hybrid Carcinoma

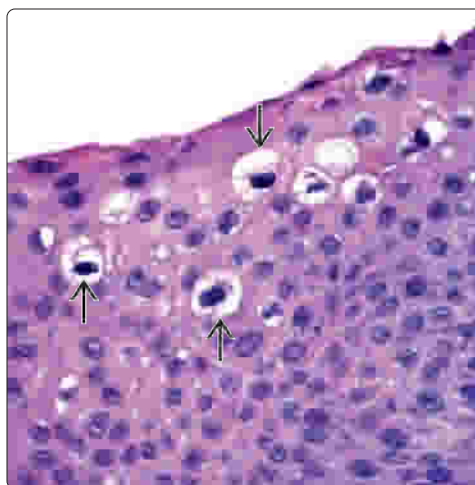


(Left) Hybrid carcinoma is a neoplasm that includes foci of VC (not shown) admixed with foci of conventional squamous cell carcinoma characterized by angulated infiltrative nests of tumor. (Right) At higher magnification, the overtly malignant cytomorphic features of the invasive SCC component are evident. The biologic risk follows that of the conventional SCC including the potential for metastatic disease. Hybrid carcinomas may occur in larynx but are more common in the oral cavity.

Squamous Papilloma



Squamous Papilloma



(Left) The differential diagnosis of VC may include squamous papilloma; however, in contrast to VC, papillomas typically lack surface keratinization and show exophytic to papillary rather than a warty appearance. (Right) Similar to VC, papillomas are composed of cytologically bland mature squamous epithelium; however, in contrast to VC, papillomas include the presence of cells showing viral-related cytopathic changes (koilocytes).

Spindle Cell "Sarcomatoid" Squamous Cell Carcinoma

KEY FACTS

TERMINOLOGY

- Squamous cell carcinoma with biphasic appearance yielding spindle cell transformation

CLINICAL ISSUES

- Male >>> female (12:1)
- Mean age: 65 years
- Strong smoking and alcohol abuse association
- Polypoid and ulcerated mass in glottis (true vocal cord, anterior commissure, posterior commissure) (~70%)
- ~80% 5-year disease-free overall survival
 - Glottic tumors have better prognosis than nonglottic tumors
 - Previous history of radiation decreases prognosis
 - Epithelial **positive** tumors have better prognosis

MACROSCOPIC

- Mean: < 2 cm; range: 0.2-8.5 cm

MICROSCOPIC

- Polypoid, pedunculated, exophytic tumor (> 98% of tumors) with surface ulceration and fibrinoid necrosis
- Imperceptible blending between squamous, spindle cells
- Storiform, solid, and fascicular architecture
- Low to intermediate cellularity most common
- Mitotic figures are easily identified, including atypical forms
- Mild to moderate pleomorphism, although isolated highly atypical cells are common
- Heterologous elements may be seen


ANCILLARY TESTS

- Epithelial immunoreactivity **absent** in up to 30% of cases
- **Positive:** CK-PAN, CK1, CK18, p63, p40

TOP DIFFERENTIAL DIAGNOSES

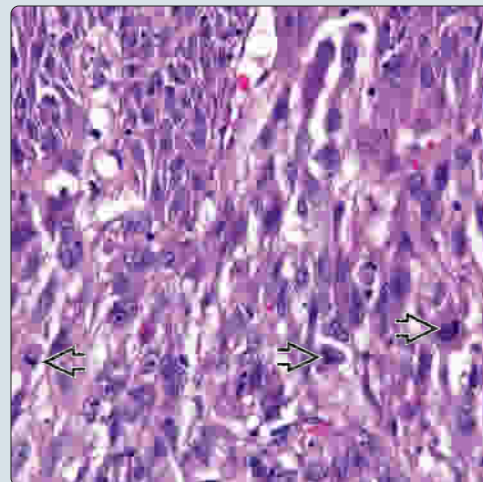
- Contact ulcer, spindle cell mucosal melanoma, fibrosarcoma, synovial sarcoma, nodular fasciitis, angiosarcoma, pleomorphic sarcoma

Polypoid Tumor Mass


(Left) H&E shows a polypoid mass with surface ulceration. The stalk leads into an area of central collagen deposition, frequently seen as a degenerative phenomenon. Surface epithelium is usually found at the polyp stalk/base. (Right) H&E shows surface epithelium transforming into a spindle cell population that blends with the surface epithelium. There are a remarkable number of mitotic figures .

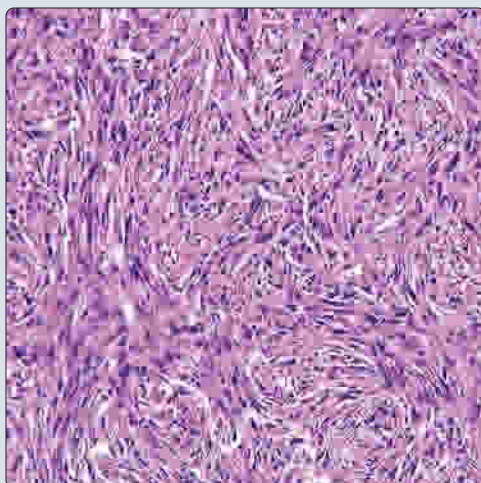


Surface Transition to Spindled Pattern

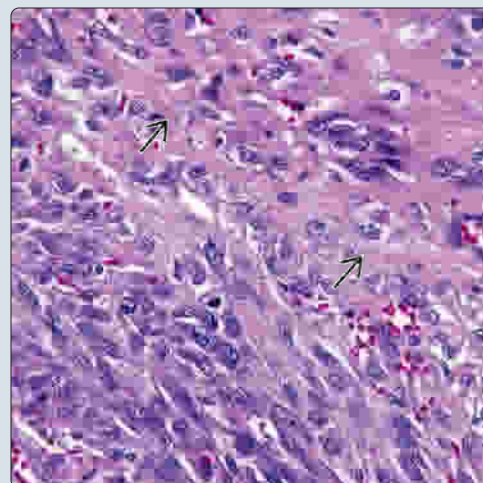


Storiform Spindled Population

(Left) H&E shows a storiform, haphazard arrangement of interlacing spindle cells. The spindle cells tend to have a high nuclear:cytoplasmic ratio and pleomorphism. (Right) Spindle cell "sarcomatoid" squamous cell carcinoma (SCSSCs) will frequently have hypocellular  areas blend with more hypercellular areas. If the tumor shows only a hypocellular pattern, it may be more difficult to diagnose as a carcinoma.



Hypo- and Hypercellular Areas



TERMINOLOGY

Abbreviations

- Spindle cell "sarcomatoid" squamous cell carcinoma (SCSSCC)

Synonyms

- Carcinosarcoma
- Spindle cell carcinoma
- Lane tumor
- Metaplastic carcinoma

Definitions

- Squamous cell carcinoma with biphasic appearance yielding spindle cell transformation

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Strong smoking association
- Strong alcohol association
- Radiation exposure occasionally reported (~ 10%)

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~ 2-3% of all laryngeal tumors
- Age
 - Mean: 65 years
 - Wide range: 30-95 years
- Sex
 - Male > > > Female (12:1)

Site

- Glottic (true vocal cord, anterior commissure, posterior commissure) (~ 70%)
- Supraglottic (15%); transglottic (12%); subglottic (2%)

Presentation

- Polypoid mass
- Hoarseness, changes in voice, sore throat, dysphagia
- Airway obstruction, shortness of breath, dyspnea
- Cough and stridor

Endoscopic Findings

- Polypoid, ulcerated mass, often attached by pedicle arising from vocal cords

Treatment

- Options, risks, complications
 - Polypectomy may be curative in many cases
 - ~ 85% of patients identified at low-stage disease
- Surgical approaches
 - Wide local excision, with additional surgery if polypectomy is insufficient
- Radiation
 - Postoperative, limited field radiation similar to grade and stage-matched squamous cell carcinoma patients (majority receive radiation)

Prognosis

- ~ 80% 5-year disease-free overall survival

- Worse prognosis
 - High-stage disease, nonglottic tumors, larger tumors, necrosis
 - Fixed vocal cords
 - Previous history of radiation
 - Epithelial **positive** immunoreactivity (perform stains for prognostic reasons)
- ~ 20% metastatic rate to regional lymph nodes
 - Usually identified in nonglottic tumors

MACROSCOPIC

General Features

- Polypoid, pedunculated, exophytic tumor (> 98%)
- Almost always ulcerated surface

Sections to Be Submitted

- Include junction of polyp with stalk: Most likely location for epithelium to be identified in ulcerated lesion

Size

- Mean: < 2 cm; range: 0.2-8.5 cm

MICROSCOPIC

Histologic Features

- Polypoid mass with surface ulceration and fibrinoid necrosis
- Areas of classic squamous cell carcinoma (surface or deep within lesion) can usually be identified, although limited
 - Dysplasia or carcinoma in situ may be seen
- Imperceptible blending between squamous and spindle cells
- Storiform, solid, and fascicular architecture
- Low to intermediate cellularity most common
 - Hypocellular lesions are very difficult to diagnose
- Tumor necrosis is limited to absent
- Mitotic figures are easily identified, including atypical forms
 - Mean: 12 mitoses/10 HPF
- Mild to moderate pleomorphism, although isolated highly atypical cells are common
- Tumor giant cells and multinucleated cells are seen
- Desmoplastic, stromal fibrosis seen in ~ 1/2 of cases
- Heterologous elements may be seen
 - Benign or malignant bone or cartilage within spindle cell population
 - Rarely, rhabdomyoblastic cells are seen
- Myxoid changes or acute inflammatory cells can be seen
- Eosinophilic cytoplasmic globules are rarely present (not part of angiosarcoma)

ANCILLARY TESTS

Immunohistochemistry

- Epithelial immunoreactivity absent in up to 30% of cases

DIFFERENTIAL DIAGNOSIS

Contact Ulcer

- Bilateral ulcerated polyps, lacking atypia with a rich vascular and inflammatory infiltrate, including mitoses

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CK-PAN	Positive	Cytoplasmic	~ 70% of cases
Vimentin	Positive	Cytoplasmic	Present in nearly 100% of cases
EMA	Positive	Cytoplasmic	Up to 20% of cases
CK1	Positive	Cytoplasmic	Up to 40% of cases
CK5/6	Positive	Cytoplasmic	~ 7% of cases
CK7	Positive	Cytoplasmic	~ 5% of cases
CK14	Positive	Cytoplasmic	~ 15% of cases
CK18	Positive	Cytoplasmic	~ 25% of cases
CK17	Positive	Cytoplasmic	~ 15% of cases
p63	Positive	Nuclear	~ 5% of cases
p40	Positive	Nuclear	~ 10% of cases
34B312	Positive	Cytoplasmic	~ 10% of cases
Actin-sm	Positive	Cytoplasmic	~ 30% of cases
S100	Positive	Nuclear & cytoplasmic	~ 5% of cases
CK4	Negative		
CK10	Negative		
CK20	Negative		
CK8/18/CAM5.2	Negative		

Spindle Cell Mucosal Melanoma

- Surface origin of atypical spindled cells, showing **positive** reactions with melanocytic markers: S100 protein, SOX10, Melan-A, HMB45

Synovial Sarcoma

- Young age at presentation, usually arising from neck soft tissues
- Epithelial and spindle cell tumor with **positive** TLE1, EMA, pan-cytokeratin
- Specific molecular alterations [t(X,18)]

Fibrosarcoma

- Herringbone arrangement of spindled cells
- Arises from soft tissues of neck rather than endoluminal tissues of larynx

Nodular Fasciitis

- Pseudosarcomatous proliferation of soft tissues adjacent to larynx
- Myxoid stroma, storiform spindle cell population with extravasated erythrocytes, keloid-like collagen, giant cells, and mitotic figures
- Actins and myofibroblastic markers **positive**; keratin **negative**

Angiosarcoma

- High-grade sarcoma with freely anastomosing vessels, atypical endothelial cells, mitoses, and cytoplasmic globules
- Reactions with vascular markers: CD34, CD31, DP-40, FLI-1

Pleomorphic Sarcoma

- Undifferentiated, high-grade sarcoma, usually arising from neck soft tissues and **not** from larynx

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Nearly always polypoid mass with surface ulceration
- **Do not** rely on epithelial marker reactivity for diagnosis

STAGING

TNM

- Most are T1 and T2 lesions (> 85%)
- Survival depends on stage and tumor location

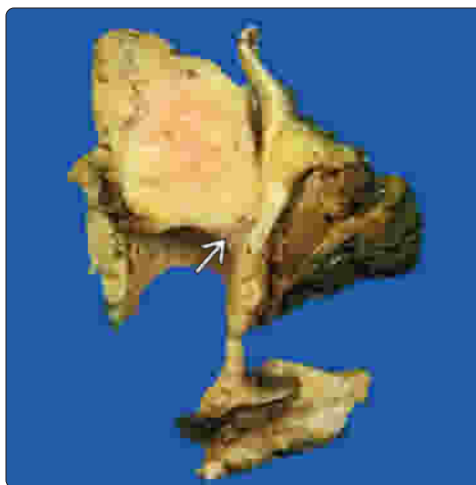
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2. Gerry D et al: Spindle cell carcinoma of the upper aerodigestive tract: an analysis of 341 cases with comparison to conventional squamous cell carcinoma. Ann Otol Rhinol Laryngol. 123(8):576-83, 2014
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5. Thompson LD et al: Spindle cell (sarcomatoid) carcinomas of the larynx: a clinicopathologic study of 187 cases. Am J Surg Pathol. 26(2):153-70, 2002
6. Lewis JE et al: Spindle cell carcinoma of the larynx: review of 26 cases including DNA content and immunohistochemistry. Hum Pathol. 28(6):664-73, 1997
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9. Hyams VJ: Spindle cell carcinoma of the larynx. Can J Otolaryngol. 4(2):307-13, 1975

Endoscopic View of Polypoid Mass

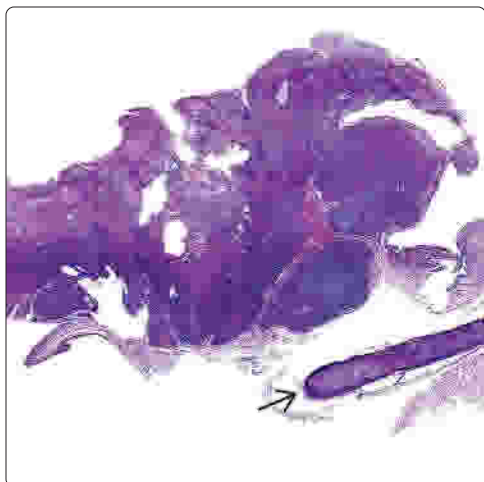


Gross Sample of Spindle Cell "Sarcomatoid" Squamous Cell Carcinoma

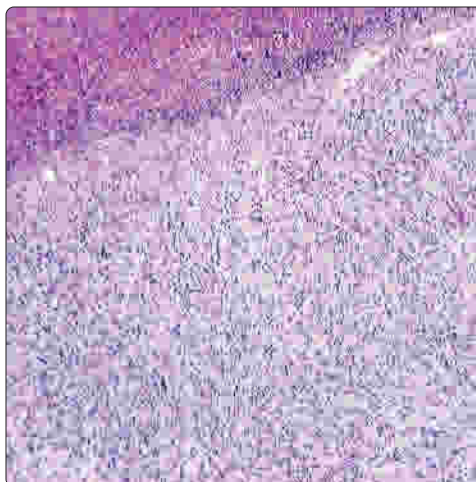


(Left) A polypoid mass is identified on the vocal cords. There is surface ulceration seen in this spindle cell squamous cell carcinoma. (Courtesy M.W. Keefe, MD.) (Right) Laryngectomy mid sagittal section shows a large polypoid tumor filling the laryngeal lumen. The tumor is attached by a very narrow pedicle or stalk, a common finding for this tumor type. (Courtesy S. Müller, DMD.)

Low Power of Polypoid Tumor



Fibrinoid Necrosis and Ulcerated Surface

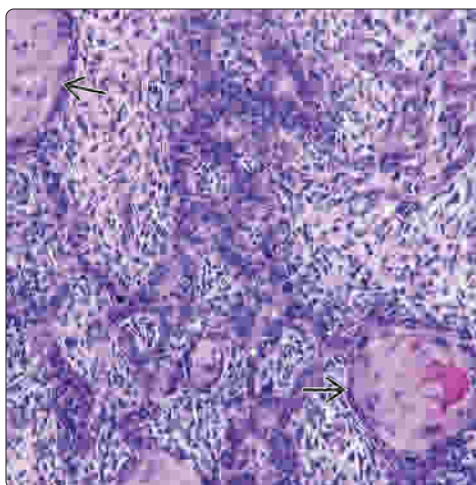


(Left) An exophytic and polypoid tumor mass expands into the larynx lumen in this example of a SCSSCC. Note the cartilage. (Right) H&E shows surface ulceration with fibrinoid necrosis subtended by an atypical spindle cell population. The cellularity is quite high and lacks a vascular proliferation.

Heavily Collagenized Stroma



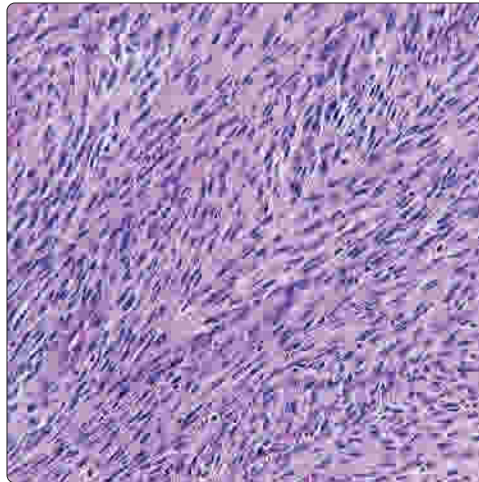
Blending of Epithelial and Spindled Cells



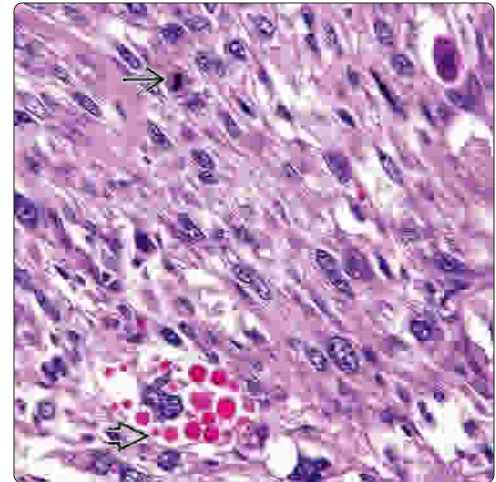
(Left) The overall polypoid shape can be seen in this SCSSCC. There is surface ulceration. The tumor is arranged in a haphazard spindled cell population, showing heavy stromal collagenization. (Right) The easily identified keratinizing squamous cell carcinoma components blend imperceptibly with the typical spindled cell population. Areas of abrupt keratinization or squamous differentiation are frequently seen in this tumor type.

(Left) H&E shows short, interlacing fascicles in a pseudo-herringbone fashion. The cells are spindled with elongated nuclei. **(Right)** H&E shows spindle cells with eosinophilic intracytoplasmic globules. The globules are nonspecific but are not seen in many other laryngeal lesions. Mitotic figures are also noted.

Short Interlacing Fascicles

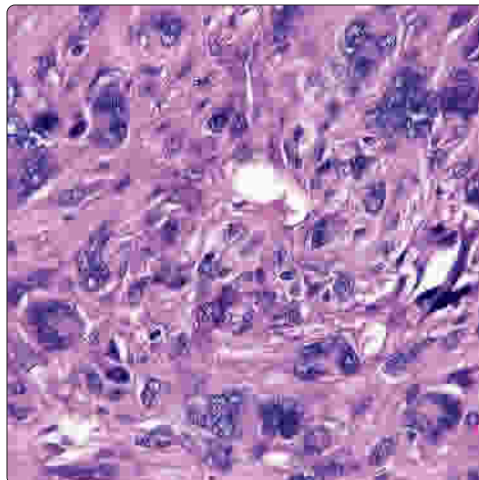


Atypical Spindled Cells With Globules

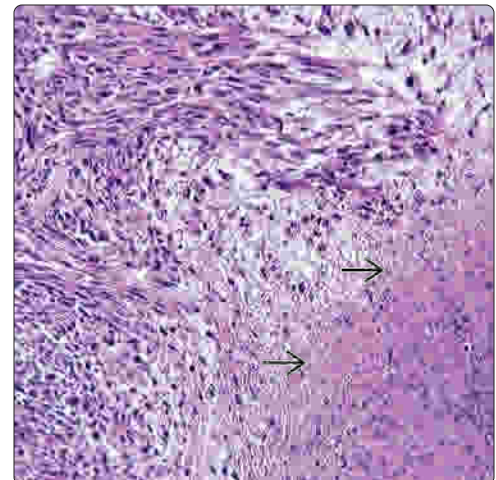


(Left) H&E shows significant pleomorphism within a spindled population. Stromal fibrosis is noted. Mitotic figures are not appreciated in this field but are generally easy to find. **(Right)** H&E shows a spindle cell population adjacent to areas of necrosis. There are areas of hypocellularity immediately adjacent to the regions of necrosis. This type of tumor necrosis is not seen in benign tumors of the larynx.

Marked Pleomorphism

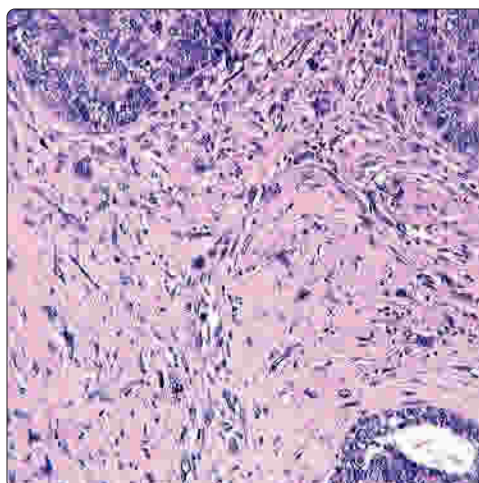


Tumor Necrosis

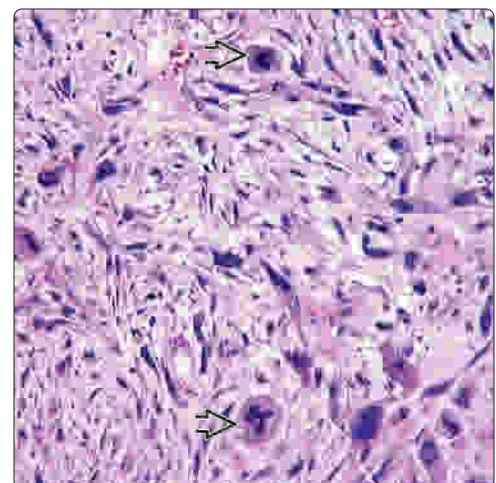


(Left) H&E shows remarkably atypical squamous epithelium with an atypical spindle cell population within the collagenized stroma. The cellularity of the spindled population is variable and ranges from hypercellular to hypocellular. **(Right)** H&E shows a haphazard to storiform arrangement of remarkably atypical spindled to stellate cells with atypical mitotic figures. The cytoplasm is opacified.

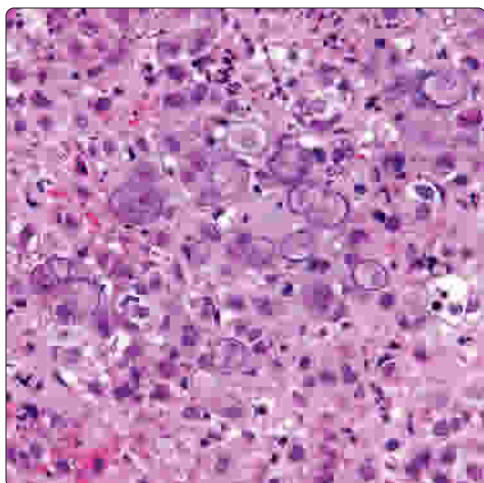
Juxtaposed Squamous and Spindled Cells



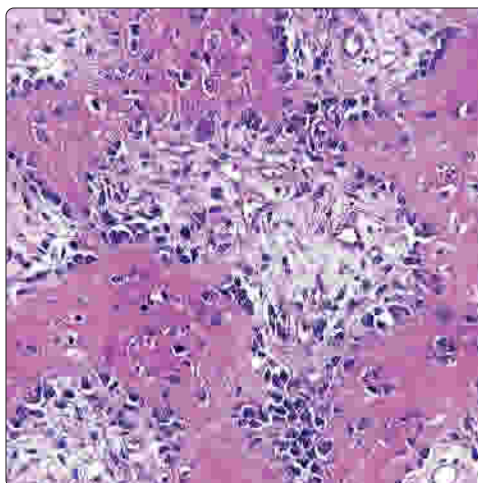
Atypical Mitoses



Chondrosarcoma Within Spindle Cell "Sarcomatoid" Squamous Cell Carcinoma

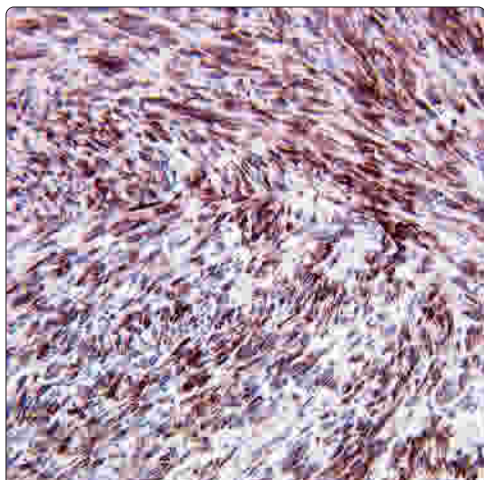


Osteosarcoma Within Spindle Cell "Sarcomatoid" Squamous Cell Carcinoma

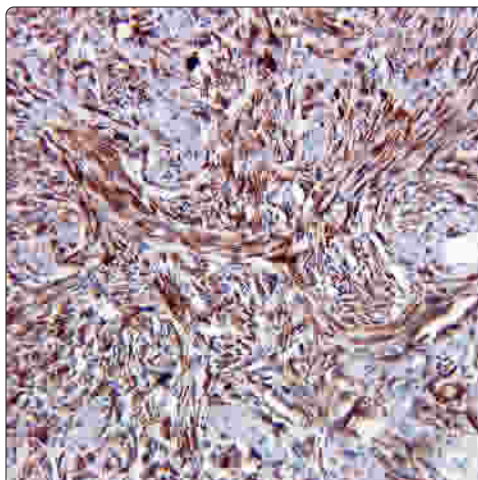


(Left) H&E shows cartilaginous differentiation within this spindle cell carcinoma. The cartilage can be malignant (chondrosarcoma) or benign (cartilage). This case shows a chondrosarcoma, separate topographically from the larynx cartilages. (Right) Heterologous elements can be seen in SCSSCC. In this field, there is malignant osteoid associated with osteoblastic activity set within an atypical spindled cell population.

CK-PAN(+) Spindled Cells



CK18 Highlights Malignant Spindle Cells

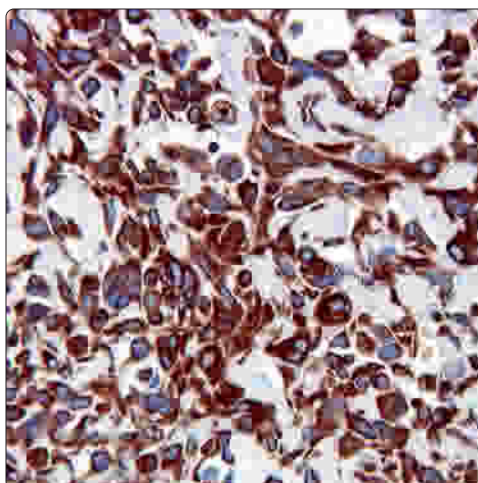



(Left) CK-PAN shows strong and diffuse cytoplasmic immunoreactivity within the spindled neoplastic cells. The spindle shape is accentuated by this study. (Right) CK18 shows strong and diffuse immunoreactivity within the spindled cells. The vessels and collagen do not stain. It is not usually necessary to perform keratin subsets to confirm the diagnosis.

p63 May Be Positive in Spindle Cell "Sarcomatoid" Squamous Cell Carcinoma



Strong Diffuse Vimentin Immunoreactivity



(Left) p63 shows a basal proliferation of positive epithelial cells , while the spindle cell population is negative. If SCSSCC, the spindle cell population may be p63 positive, but it is not a common occurrence. (Right) Vimentin shows heavy and diffuse cytoplasmic immunoreactivity within the atypical spindle and polygonal population. Vimentin can be used to test the tumor tissue antigenicity also but does not help to separate between tumor types of the larynx.

Basaloid Squamous Cell Carcinoma

KEY FACTS

TERMINOLOGY

- Variant of squamous cell carcinoma (SCC) showing predominantly basaloid cells with associated squamous differentiation (keratinization, dysplasia, in situ, or invasive tumor)

ETIOLOGY/PATHOGENESIS

- High frequency of tobacco and alcohol use
- May show p16/HPV ISH association

CLINICAL ISSUES

- Male >> female
- Mean age: 6th-7th decades
- Hypopharynx, supraglottic or transglottic (larynx)
- Regional and distant metastases are common with higher stage at presentation than other forms of SCC
- Radical surgery with combination chemoradiation

MACROSCOPIC

- Hard, white-tan mass associated with central necrosis

MICROSCOPIC

- Basaloid neoplasm arranged in many patterns with cells showing high nuclear:cytoplasmic ratio
- Lobules of tumor with peripherally palisaded cells showing comedonecrosis and high mitotic index
- Limited areas of squamous differentiation (dysplastic surface epithelium, abrupt keratinization, keratin pearl formation, SCC in situ, invasive SCC)
- Occasional mucohyaline type material may be seen

ANCILLARY TESTS

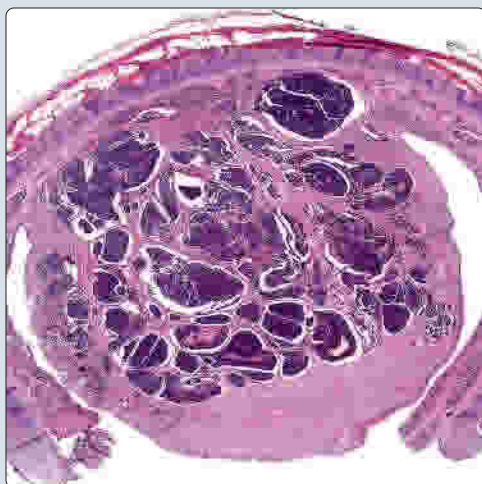
- **Positive:** Epithelial markers; > 50% Ki-67
- p16 and HPV ISH variably expressed, site dependent

TOP DIFFERENTIAL DIAGNOSES

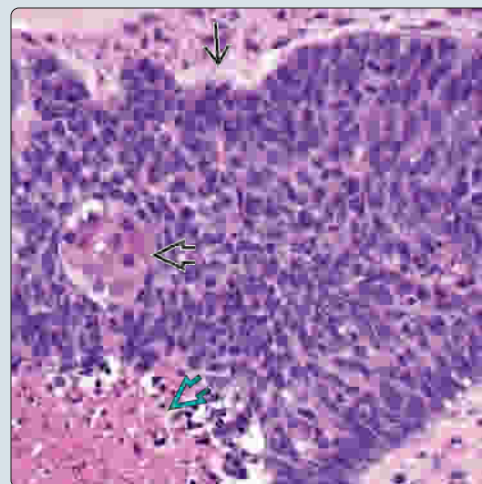
- Oropharyngeal carcinoma, squamous cell carcinoma, adenoid cystic carcinoma, basal cell adenoma/adenocarcinoma, atypical carcinoid/small cell carcinoma, *NOTCH1* midline carcinoma

Luminal Basaloid Squamous Cell Carcinoma of Larynx

(Left) There is a polypoid projection into the laryngeal lumen of this BSCC. There is a tumor deep within the polyp, showing a dark, basaloid appearance at low power. (Right) There is a basaloid neoplastic proliferation with peripheral palisading of the nuclei, with partial "clefing" artifact [A]. An island of abrupt squamous differentiation [B] is seen adjacent to central comedonecrosis [C].



Abrupt Squamous Eddies and Necrosis

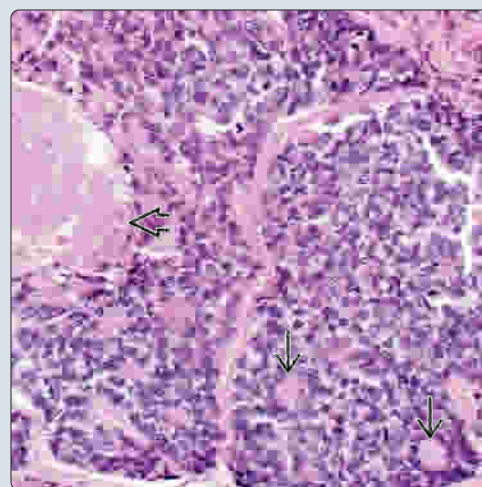


Lobules of Neoplastic Basaloid Cells

(Left) Hematoxylin and eosin shows intact surface mucosa. The basaloid proliferation demonstrates a lobular growth with peripheral palisading of the cells and central comedonecrosis [A]. (Right) Basaloid squamous proliferation with areas of comedonecrosis [B] is shown here. There are several small mucohyaline globules [C] within the proliferation. The differential with adenoid cystic carcinoma is raised in this setting.



Mucohyaline Globules



TERMINOLOGY

Abbreviations

- Basaloid squamous cell carcinoma (BSCC)

Definitions

- Rare, distinct variant of SCC showing predominantly basaloid cells with associated squamous differentiation (keratinization, dysplasia, in situ, or invasive tumor)

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- High frequency of tobacco and alcohol use

CLINICAL ISSUES

Epidemiology

- Age
 - Mean: 6th-7th decades
- Sex
 - Male > > female

Site

- Piriform sinus > oropharynx ~ larynx

Presentation

- Dysphagia, pain, cough, hemoptysis, neck mass
- Frequently shows multifocal disease

Treatment

- Radical surgery with combination chemoradiation

Prognosis

- Regional and distant metastases are common with higher stage at presentation than other forms of SCC
- Appears biologically more aggressive, although stage- and HPV-status dependent
 - Majority of patients die of disease in < 3 years
 - Better prognosis for HPV associated tumors

MACROSCOPIC

General Features

- Hard, white-tan mass associated with central necrosis
- Up to 6 cm

MICROSCOPIC

Histologic Features

- Basaloid neoplasm arranged in many patterns, but smooth contoured lobules predominate
 - Solid, lobular, cords, cribriform, cystic, glandular
- Peripherally palisaded cells with high N:C ratio and vesicular-round nuclei
- Comedonecrosis within lobules; high mitotic index
- Occasional mucohyaline type material may be seen
- Squamous differentiation, usually limited in degree
 - Dysplastic surface epithelium, abrupt keratinization, keratin pearl formation, SCC in situ, invasive SCC
- Rosettes may be seen; ~ 5% may have spindle component

ANCILLARY TESTS

Immunohistochemistry

- Positive:** Epithelial markers; > 50% Ki-67
 - p16 and HPV ISH variably expressed, site dependent
- Negative:** Chromogranin, synaptophysin, CD56, EBER

DIFFERENTIAL DIAGNOSIS

Oropharyngeal Carcinoma

- Basaloid appearance, lymphoid stroma, nonkeratinizing, limited necrosis; usually strong p16

Squamous Cell Carcinoma

- Superficial, shallow biopsies may miss basaloid component

Adenoid Cystic Carcinoma

- Prominent cribriform pattern, angulated nuclei, no nucleoli, lacks squamous differentiation; S100 protein (+)

Basal Cell Adenoma/Adenocarcinoma

- Basaloid proliferation with reduplicated basement membrane material, lacking squamous features

Midline Carcinoma, Including *NUTM1*

- Younger age, midline presentation, abrupt keratinization, NUTM1 immunohistochemistry

SELECTED REFERENCES

- Fritsch VA et al: Basaloid squamous cell carcinoma of the larynx: analysis of 145 cases with comparison to conventional squamous cell carcinoma. *Head Neck*. 36(2):164-70, 2014

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CK5/6	Positive	Cell membrane and cytoplasm	
p63	Positive	Nuclear	
p40	Positive	Nuclear	
EMA	Positive	Cytoplasmic	
p53	Positive	Nuclear	
p16	Positive	Nuclear & cytoplasmic	Selected cases
CEA-M	Positive	Cytoplasmic	~ 50% of cases
CK7	Negative		

Exophytic and Papillary Squamous Cell Carcinoma

KEY FACTS

TERMINOLOGY

- Exophytic squamous cell carcinoma (ESCC) is characterized by broad, cauliflower-like projections of malignant squamous epithelium
- Papillary squamous cell carcinoma (PSCC) is characterized by delicate, stalk-like papillary growth of malignant squamous epithelium

ETIOLOGY/PATHOGENESIS

- Tobacco (smoking) and alcohol abuse
- HPV present in 15-20% of cases (types 6 or 16)

CLINICAL ISSUES

- Male >> female (4:1)
- Supraglottis >> glottis >> subglottis
- Multifocality (synchronous or metachronous) common
- Most tumors present at low tumor stage (T1 or T2)
- Recurrences develop (~ 1/3 of patients)

MICROSCOPIC

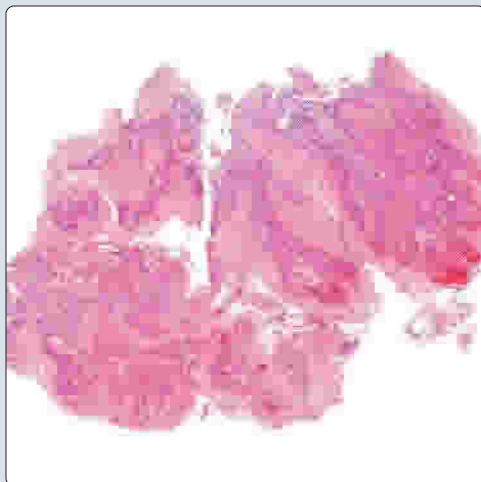
- Squamous cell carcinoma (SCC) demonstrating dominant (> 70%) exophytic or papillary architecture
- Exophytic** pattern
 - Broad-based, bulbous exophytic growth, with rounded projections
- Papillary** pattern
 - Multiple, thin, delicate, filiform projections with fibrovascular core
- Stromal invasion can be found
- Architectural distortion with loss of cellular polarity
- Nuclear enlargement, increased nuclear:cytoplasmic ratio, prominent nucleoli
- Numerous mitotic figures, including atypical forms

TOP DIFFERENTIAL DIAGNOSES

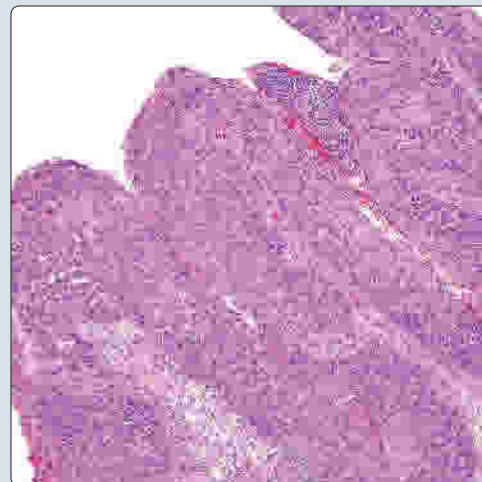
- Verrucous squamous cell carcinoma
- Carcinoma in situ
- Papillary hyperplasia or squamous papilloma

Papillary: Fibrovascular Cores

(Left) Papillary squamous cell carcinoma (SCC) is frequently sectioned tangentially, creating an end-on appearance. Generally, more than 70% of the proliferation is papillary, with delicate fibrovascular cores. **(Right)** Each papillary projection surrounding a fibrovascular core shows a remarkable pleomorphism. There is architectural disarray with increased cellularity and increased mitoses.

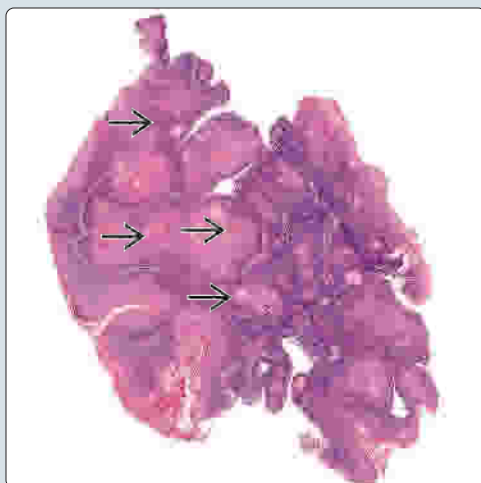


Papillary: Marked Pleomorphism



Exophytic: Broad, Bulbous Projections

(Left) The outer contour of this carcinoma shows a cauliflower-like appearance, although numerous fibrovascular cores [X] are easily identified within the tumor. This is characteristic for an exophytic pattern SCC. **(Right)** The bulbous projections of the exophytic SCC show the surface epithelium on either side of this broad projection. There is parakeratosis [X] and dyskeratosis. There is a suggestion of maturation toward the surface of this tumor.



Exophytic: Atypical Epithelium



TERMINOLOGY

Abbreviations

- Exophytic squamous cell carcinoma (ESCC)
- Papillary squamous cell carcinoma (PSCC)

Definitions

- ESCC is characterized by broad, cauliflower-like projections of malignant squamous epithelium
- PSCC is characterized by delicate, stalk-like papillary growth of malignant squamous epithelium

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Tobacco use (smoking) and alcohol use
- Human papillomavirus (HPV) is etiologic factor in ~ 15-20% of cases

Malignant Transformation

- Malignant transformation from squamous papilloma

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon variant of squamous cell carcinoma (SCC)
- Age
 - Mean: 6th and 7th decades
- Sex
 - Male > > female (4:1)

Site

- Supraglottis > > glottis > > subglottis

Presentation

- Hoarseness; airway obstruction; rarely dysphagia, sore throat, cough, hemoptysis
- Multifocality (synchronous or metachronous) common

Treatment

- Complete excision: Excisional biopsy, vocal cord stripping
 - Laryngectomy reserved for recalcitrant cases
- Postoperative radiation for most patients

Prognosis

- PSCC and ESCC have better prognosis than squamous cell carcinoma, not otherwise specified (SCC, NOS)
- Recurrences develop (~ 1/3 of patients)
- Most tumors present at low tumor stage (T1 or T2)

MACROSCOPIC

General Features

- Polypoid, exophytic, bulky, papillary, or fungiform tumors arising from broad-based or narrow, thin pedicle

Size

- **ESCC:** Mean: 1.5 cm; **PSCC:** Mean: 1 cm

MICROSCOPIC

Histologic Features

- Neoplastic squamous epithelial proliferation demonstrating dominant (> 70%) exophytic or papillary architecture

- Patterns may overlap and coexist
 - When overlapping, ESCC is default
- Unequivocal cytomorphologic evidence of malignancy
 - Limited surface keratosis
 - Architectural distortion with loss of cellular polarity
 - Nuclear enlargement, increased nuclear:cytoplasmic ratio, prominent nucleoli
 - Frequently immature, basaloid phenotype
 - Numerous mitotic figures, including atypical forms
 - Focal necrosis can be found
- Stromal invasion may be found
 - May require serial sections or reorientation to demonstrate invasion
 - Invasion is usually superficial, lacking perineural, vascular, or chondroosseous invasion
 - Cohesive nests or single cell infiltration, associated with inflammation
- Koilocytic atypia is frequently noted
 - Hyperchromatic, crenated nucleus surrounded by clear halo with prominent cell border

Papillary

- Multiple, thin, delicate, filiform, finger-like papillary projections
- Papillae contain delicate fibrovascular core surrounded by neoplastic epithelium
- Tangential sectioning yields "bunch of celery" cut across the stalk

Exophytic

- Broad-based, bulbous exophytic growth
- Projections are rounded and cauliflower-like
- Tangential sectioning yields number of central fibrovascular cores with lobular periphery

DIFFERENTIAL DIAGNOSIS

Verrucous Squamous Cell Carcinoma

- Broad, pushing border of infiltration with parakeratotic crypting, church spire keratosis
- Maturation, limited pleomorphism, and limited mitotic figures

Carcinoma In Situ

- Atypical epithelial proliferation without forming appreciable clinical lesion
- Invasion may be difficult to assess, especially in tangentially sectioned tumors
 - If questionable, large tumor weighs heavily toward invasive carcinoma


Squamous Papilloma

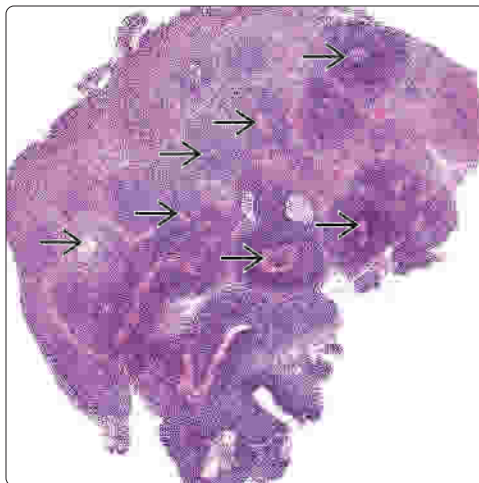
- Noncomplex papillae; lacks pleomorphism, invasion, necrosis, atypical mitoses

SELECTED REFERENCES

1. Cobo F et al: Review article: relationship of human papillomavirus with papillary squamous cell carcinoma of the upper aerodigestive tract: a review. *Int J Surg Pathol.* 16(2):127-36, 2008
2. Ereno C et al: Papillary squamous cell carcinoma of the larynx. *J Laryngol Otol.* 115(2):164-6, 2001
3. Thompson LD et al: Exophytic and papillary squamous cell carcinomas of the larynx: A clinicopathologic series of 104 cases. *Otolaryngol Head Neck Surg.* 120(5):718-24, 1999

Exophytic: Broad Papillary Projections


(Left) An exophytic SCC shows a smooth exterior. However, multiple fibrovascular cores  are noted extending toward the surface of this neoplasm. This needs to be the dominant pattern in order to diagnose this variant of SCC. **(Right)** In many examples of exophytic SCC, there is a round to cauliflower-like appearance to the proliferation. However, high power shows pleomorphism and increased mitoses.

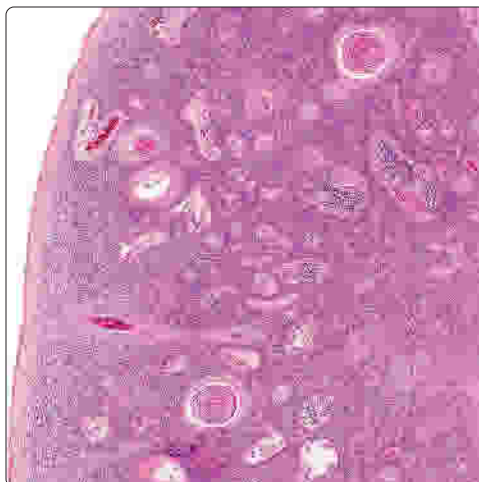


Exophytic: Rounded Surface

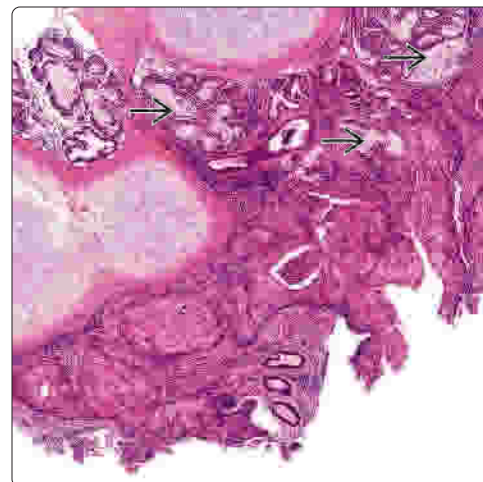


Exophytic: Smooth Contour



(Left) There is a well-defined border to the edge of this exophytic type SCC. However, there is easily identified pleomorphism throughout, with increased cellularity and architectural disorder. **(Right)** An exophytic pattern to this SCC is shown. However, invasion was present in this part of the sample, showing extension down to the cartilage. Note the minor mucoserous glands  focally surrounded by the neoplastic proliferation.

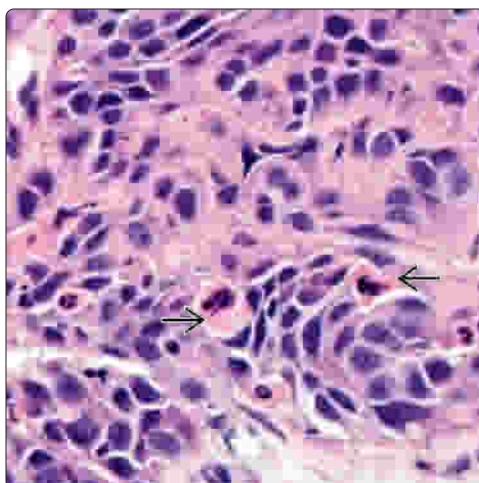


Exophytic: Cartilage Invasion

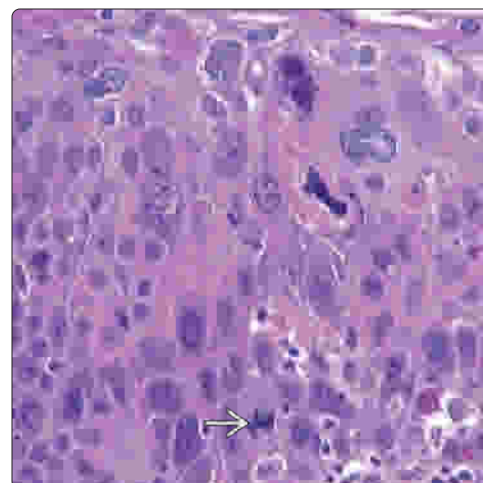


Pleomorphism With Dyskeratosis

(Left) This high-power view shows a highly atypical squamous epithelium with dyskeratosis , architectural disarray, and lack of polarization, along with nuclear hyperchromasia and pleomorphism. **(Right)** The cytomorphonuclear features of carcinoma are usually easily recognized. There is an atypical mitotic figure , lack of maturation toward the surface, profound nuclear pleomorphism, and increased nuclear:cytoplasmic ratio. Dyskeratosis is also present.



Marked Dysmaturation and Pleomorphism



Papillary: Multiple Filiform Projections

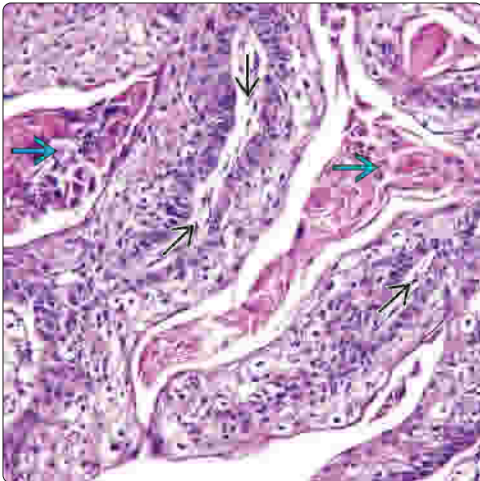


Papillary: Central Fibrovascular Core

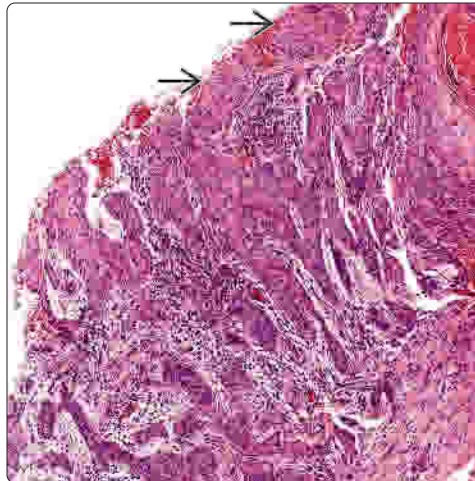


(Left) Multiple, delicate, filiform papillary projections are crowded together in this papillary SCC. Tangentially, sections still demonstrate numerous projections toward the periphery of the tumor. Fibrovascular cores are thin. **(Right)** A papillary projection shows a central fibrovascular core that is surrounded by a highly atypical squamous proliferation in this papillary SCC. There is loss of maturation, focal surface keratosis, and increased mitotic figures.

Papillary: Complex Papillary Structures

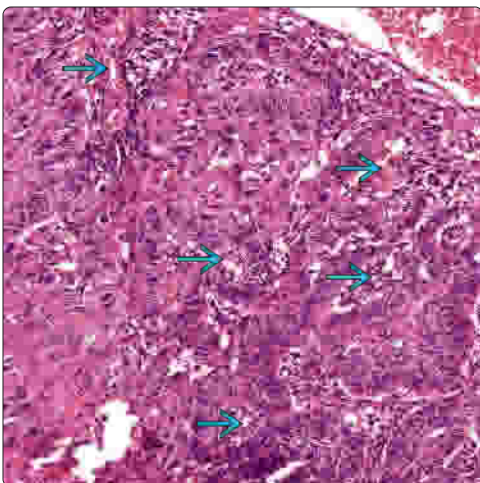


Papillary: Tangential Sectioning of Papillae

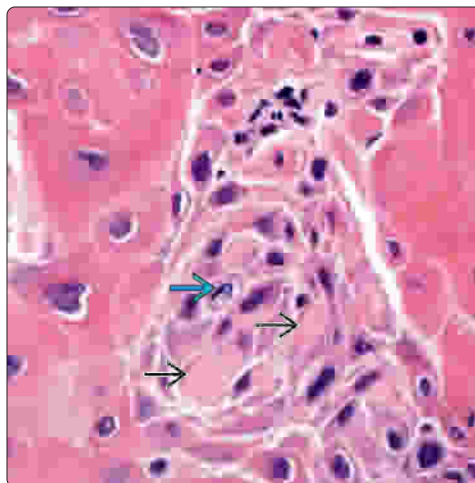


(Left) Multiple delicate, finger-like or filiform papillary projections comprise this papillary SCC. There is parakeratosis and keratin debris between the papillae. The fibrovascular cores are delicate and thin. **(Right)** At the surface of this papillary SCC, the epithelium shows nests and finger-like projections of the neoplastic epithelium into the stroma. These areas qualify for invasion. Note the surface erosion.

Papillary: Pleomorphism Cytologically



Dyskeratosis and Parakeratosis



(Left) There are numerous delicate papillary projections surrounding fibrovascular cores in this papillary SCC. The epithelium shows significant pleomorphism, dyskeratosis, lack of maturation, and mitotic figures. However, invasion is difficult to prove. **(Right)** The abnormal keratinization is seen on either side of the central part of the papillary projection. There is dyskeratosis and a mitotic figure in this papillary SCC. Pleomorphism is moderate.

Adenosquamous Carcinoma

KEY FACTS

TERMINOLOGY

- Tumor that demonstrates admixture of biphasic components of true adenocarcinoma carcinoma (ASC) and squamous cell carcinoma (SCC)

CLINICAL ISSUES

- Rare, < 1% of SCC
- Lymph node metastases at presentation (up to 75%)
- Aggressive surgery required, including neck dissection
- Poor prognosis (5-year survival: 15-25%)
- Usually older age at initial presentation
- Male > female (2:1)

MACROSCOPIC

- Exophytic, polypoid mass to indurated submucosal nodule, often with ulceration, ~ 1 cm

MICROSCOPIC

- Biphasic appearance of separate or blended tumors, showing areas of transition

- SCC component can be in situ or invasive
- Adenocarcinoma identified away from surface
 - Tubular, alveolar, or glandular
 - Mucin (intraluminal or intracellular) may be seen (not required)
- Undifferentiated or "intermediate" transitional cells can be seen, often with clear cytoplasm
- Metastases may display both components

ANCILLARY TESTS

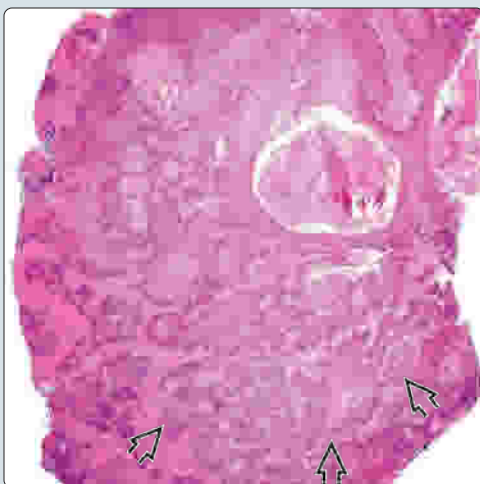
- Adenocarcinoma usually CK7 and CEA(+)
- SCC is CK5/6, p63, and p40(+)
- p16 (> 70% strong, diffuse, nuclear and cytoplasmic (+) in ~ 30% of cases) in squamous and glandular components

TOP DIFFERENTIAL DIAGNOSES

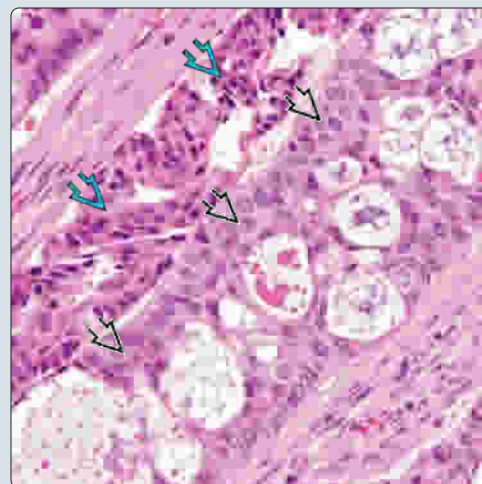
- Mucoepidermoid carcinoma, acantholytic SCC, basaloid SCC, concurrent tumors, adenocarcinoma with squamous metaplasia, necrotizing sialometaplasia

Adenosquamous Carcinoma With Admixture of Both Elements

(Left) This low-power view of a larynx tumor demonstrates a mixture of squamous cell carcinoma (SCC) and adenocarcinoma in the same biopsy. The SCC is more toward the surface, while the adenocarcinoma is deeper in the biopsy. (Right) The close proximity of the glandular and squamous components of this adenosquamous carcinoma is striking; the squamous cell component shows dyskeratosis and opaque cytoplasm, while the adenocarcinoma component shows mucinous material.

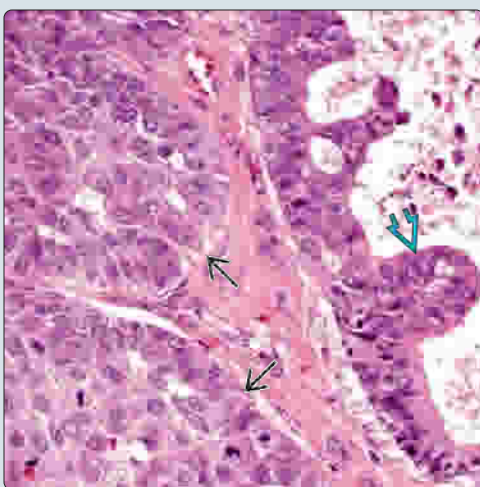


Intimate Admixture of Components

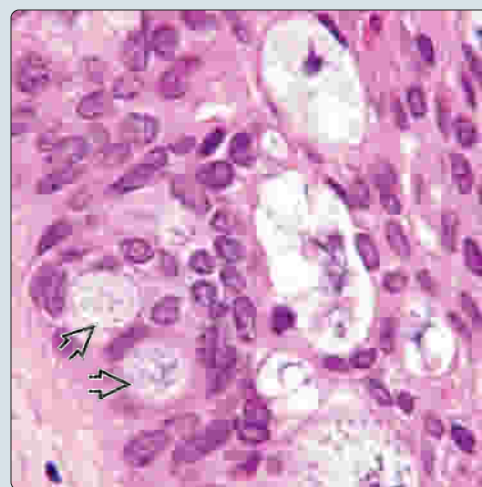


Papillary Glandular and Pavemented Squamous Differentiation

(Left) There are 2 tumor morphologies in this high-power of ASC. The SCC shows intercellular bridges and keratinization, while the adenocarcinoma shows papillary projections into a cystic lumen. (Right) The squamous cell carcinoma component is in direct approximation of the adenocarcinoma portion of this tumor. Note the mucin production, confirming the adenocarcinoma portion of the tumor.



Blended Squamous and Glandular Profiles



TERMINOLOGY

Abbreviations

- Adenosquamous carcinoma (ASC)

Definitions

- Tumor that demonstrates admixture of biphasic components of true adenocarcinoma and squamous cell carcinoma (SCC)
 - Some considered it to be a high-grade mucoepidermoid carcinoma

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Cigarette smoking and alcohol consumption implicated
- Role of gastroesophageal reflux is not as well established

Pathogenesis

- AC originates from basal cells of surface epithelium that are capable of divergent differentiation

CLINICAL ISSUES

Epidemiology

- Incidence
 - While > 90% of all head and neck mucosal malignancies are SSC, < 1% of these tumors are adenosquamous carcinoma
- Age
 - Usually older age at initial presentation
 - Mean: 6th-7th decades
- Sex
 - Male > female (2:1)

Site

- Any region of larynx, with hypopharynx occasionally affected
- May also present in oral cavity (~ 22%), sinonasal tract (~ 17%), and oropharynx (~ 17%)

Presentation

- Hoarseness, sore throat, dysphagia
- Hemoptysis
- Neck lymph node metastases in up to 75% of patients at presentation
- Sinonasal tract and oral cavity symptoms are also nonspecific

Treatment

- Surgical approaches
 - Aggressive surgery required
 - Neck dissection may be warranted even without clinical disease
- Drugs
 - Chemotherapy employed for metastatic disease
- Radiation
 - Radiation combined with surgery can yield benefit

Prognosis

- Poor prognosis
 - Significantly worse than conventional SCC

- If HPV-related and oropharynx location, do much better clinically
- 5-year survival: 15-25%
 - 2-year survival: 55%
- Majority of patients present with lymph node metastases
 - Mean: 65%
- Most patients present with high-stage disease
 - Stage is predictive of outcome
 - However, multivariate analysis between stage and tumor type is unavailable
- Distant metastases develop in ~ 25% of patients
 - Most commonly to lungs, followed by bones

MACROSCOPIC

General Features

- Exophytic mass
- Polypoid mass
- Poorly defined indurated submucosal nodule
- Ulceration is frequent

Size

- Mean: ~ 1 cm
 - Can be up to 6.5 cm in maximum dimension

MICROSCOPIC

Histologic Features

- Admixture of both true adenocarcinoma and SCC
 - Biphasic appearance
- Can be distinct, separate tumors in close proximity, but many are blended, intermixed, and commingled, showing areas of transition
- SCC component can be in situ or invasive
 - Tumors can be well to poorly differentiated
 - Squamous differentiation confirmed
 - Pavemented growth
 - Intercellular bridges
 - Keratin pearl formation
 - Dyskeratosis
 - Individual cell keratinization
- Adenocarcinoma tends to develop deep in tumor (away from surface)
 - Tubular structures that give rise to glands within glands, alveolar to glandular
 - Adenocarcinoma cells can be basaloid
 - Separation from basaloid SCC can be arbitrary
 - Mucin production is typically present (intraluminal or intracellular), but not required
 - Rarely, signet ring cells may be present
- Undifferentiated or intermediate transitional cells can be seen, often with clear cytoplasm
- Both components may have
 - Necrosis
 - Increased mitotic figures
 - Perineural invasion
 - Angiolymphatic invasion
- Tends to have sparse inflammatory cell infiltrate
- Desmoplastic stromal response is usually minimal to absent
- Concurrent necrotizing sialometaplasia may be seen

- Can be difficult to separate reactive from neoplastic, especially on superficial biopsies
- Metastases may display both components although one usually predominates

ANCILLARY TESTS

Histochemistry

- Mucicarmine (+)
 - In adenocarcinoma component only

Immunohistochemistry

- Generally, **positive** in both components with high molecular weight cytokeratins
- Glandular component expresses
 - CEA
 - Low molecular weight cytokeratins
 - Specifically, CK7 is **positive**
 - CK20 is **negative**
- Squamous cell component usually expresses
 - CK5/6, p63, p40
- p16 (> 70% strong, diffuse, nuclear and cytoplasmic [+]) in ~ 30% of cases) in squamous and glandular components
- HPV DNA present in ~ 30% of cases (although not always same as p16[+] cases)

Flow Cytometry

- High prevalence of aneuploidy has been demonstrated

Electron Microscopy

- Features of both squamous and glandular differentiation are present

DIFFERENTIAL DIAGNOSIS

Mucoepidermoid Carcinoma

- Mucoepidermoid carcinoma (MEC) has much better prognosis than ASC
- Does not have surface component
 - Lacks dysplasia or carcinoma in situ
- MEC lacks true squamous cell differentiation, showing intermediate cells
- No true adenocarcinoma adjacent to epidermoid component in MEC
- True mucocytes (squashed, eccentric nucleus) rare in adenosquamous carcinoma
- Separation may be impossible in some cases
 - Some view adenosquamous cell carcinoma as high-grade MEC

Acantholytic (Adenoid) Squamous Cell Carcinoma

- Acantholysis or dilapidated appearance can mimic adenocarcinoma
- Mucin in true glandular spaces is not seen in acantholytic SCC, thus it is adenoid type

Basaloid Squamous Cell Carcinoma

- Dominant pattern of growth is basaloid cells
- Peripheral nuclear palisading usually present
- Squamous differentiation
 - May have isolated keratinization, squamous metaplasia without atypia or SCC
- No intra- and extracellular mucin

- These cases may show p16 &/or HPV ISH positivity (oropharynx especially)

Concurrent Tumors

- Requires identification of two topographically separate tumors, one an adenocarcinoma, one a SCC

Adenocarcinoma With Squamous Metaplasia

- Absence of malignant appearance to squamous component
- Usually isolated and minor component of tumor

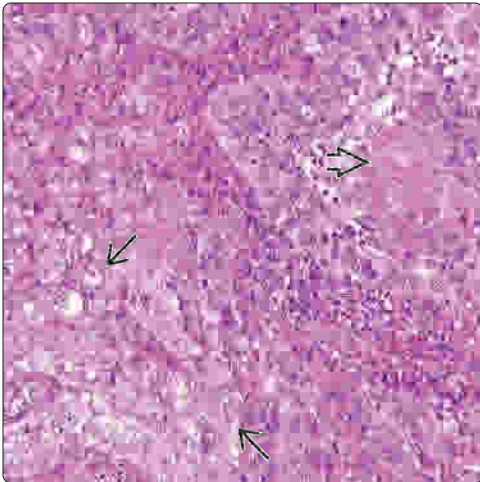
Necrotizing Sialometaplasia

- Metaplastic squamous cells can extend down gland-duct units, entrapping minor mucoserous glands
 - Glandular component appears benign
- Preservation of lobular, gland architecture (especially on low power)
- Areas of necrosis or inflammation are common
- Cellular atypia may be present, but frank pleomorphism is absent

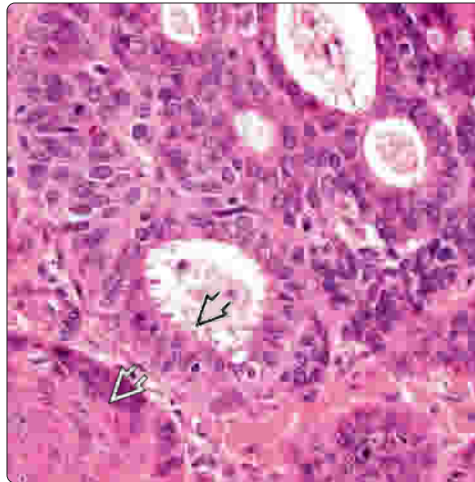
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Various Degrees of Differentiation

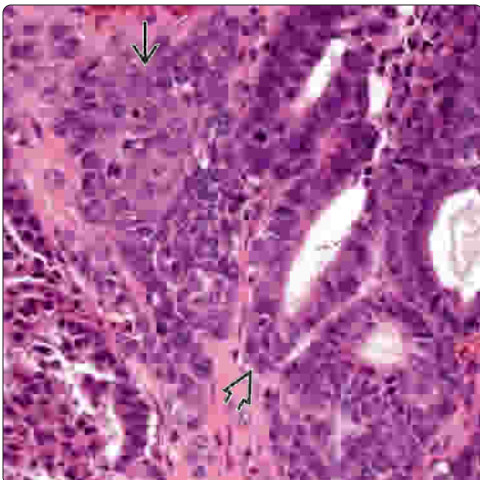


Glands in the Adenocarcinoma Component

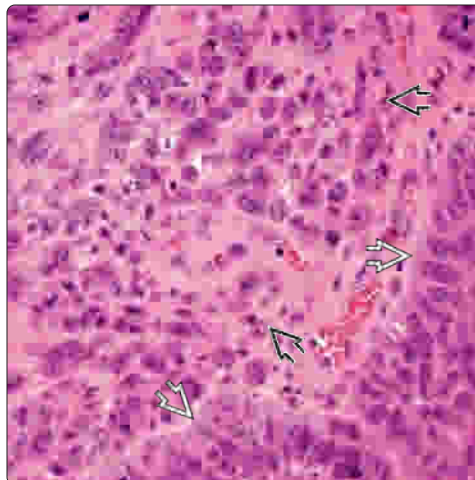


(Left) There is a remarkable blending of the tumors in this example, with an intermediate or undifferentiated component in between. The squamous elements are highlighted by the keratin pearl formation [X], while the more undifferentiated component has clearing of the cytoplasm [X]. (Right) The adenocarcinoma component shows well-formed glands with blebs on the surface [X], along with inspissated material. An area of squamous carcinoma is noted [X] immediately adjacent.

Distinct But Blended Morphologies

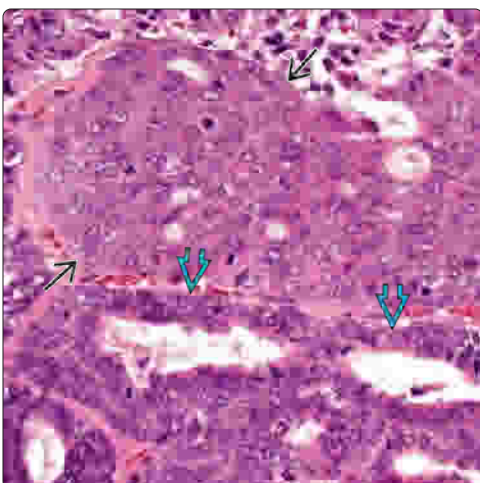


Individual Infiltration and Sheet-Like Distribution



(Left) There are distinct populations (adenocarcinoma [X], SCC [X]) in this ASC, and yet they show a very intimate and blended appearance. (Right) Two different carcinoma types are seen. The adenocarcinoma [X] shows a sheet to glandular profile of cells with prominent nucleoli. The SCC [X] shows a pavement appearance.

Differing Morphologies in Adenosquamous Carcinoma



Mucicarmine (+) Secretions



(Left) There are 2 distinct morphologies in this field of ASC. The SCC [X] shows opacified cytoplasm and a paved growth, while the adenocarcinoma component [X] shows a glandular morphology with cuboidal/columnar cells. (Right) The mucicarmine stain highlights mucinous material within the lumen of a number of the islands of adenocarcinoma [X], while no reaction is noted in the squamous epithelium [X].

KEY FACTS

TERMINOLOGY

- Heterogeneous group of malignant neoplasms characterized by presence of epithelial and neuroendocrine differentiation with prognosis predicated on tumor type
- Classification of NECs of head and neck includes
 - Typical carcinoid
 - Atypical carcinoid
 - Small cell carcinoma
 - Large cell neuroendocrine carcinoma (LCNEC)

CLINICAL ISSUES

- Uncommon tumors, but in order of frequency: Atypical carcinoid > small cell carcinoma > LCNEC > typical carcinoid
- Larynx is most common site of occurrence
 - Supraglottic larynx most common single site of occurrence
- Typical carcinoid excellent behavior generally cured following surgical resection
- Atypical carcinoid: 48% 5-year survival; 30% 10-year survival

- Small cell carcinoma: Poor prognosis 16% 2-year survival; 5% 5-year survival; 19% 5-year disease-specific survival)
- LCNEC: Commonly presents with advanced stage (stages III and IV); 15-21% 5-year disease-specific survival

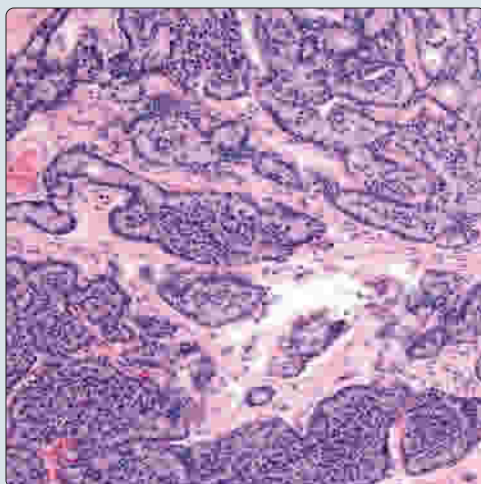
MICROSCOPIC

- All NECs are submucosal tumors showing variety of growth patterns, including organoid, trabecular, ribbons, cribriform or solid growth
- All have cells with stippled (salt and pepper) nuclear chromatin pattern except LCNEC which has large nuclei with vesicular chromatin
- Variable degree of nuclear pleomorphism and mitotic activity per histologic type

ANCILLARY TESTS

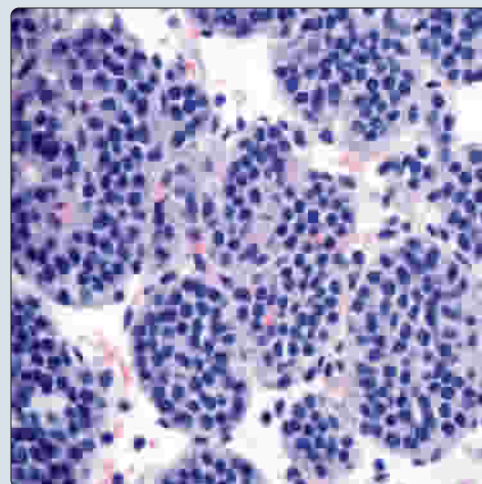
- All NECs variably immunoreactive for cytokeratins (AE1/AE3, CAM5.2) that may include punctate paranuclear staining, and neuroendocrine markers
- Atypical carcinoid immunoreactive for calcitonin

Typical Carcinoid, Growth Pattern

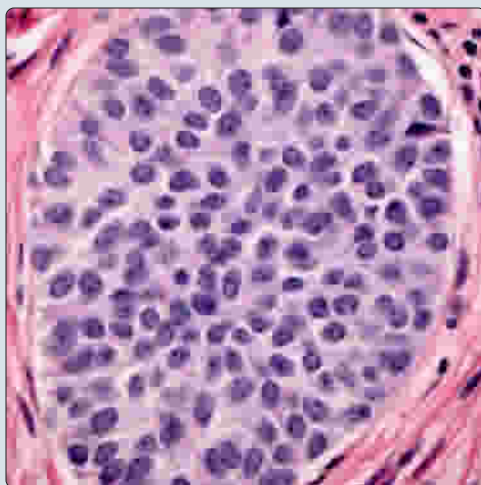


(Left) Laryngeal typical carcinoid consists of a submucosal cellular neoplasm showing trabecular, solid, and organoid growth patterns. Such patterns of growth are characteristic, although not unique, for neuroendocrine neoplasms. (Right) Lobular nests of tumor are composed of cells with uniform-appearing round to oval nuclei with dispersed nuclear chromatin and absence of nuclear pleomorphism and mitotic activity.

Typical Carcinoid, Lobules

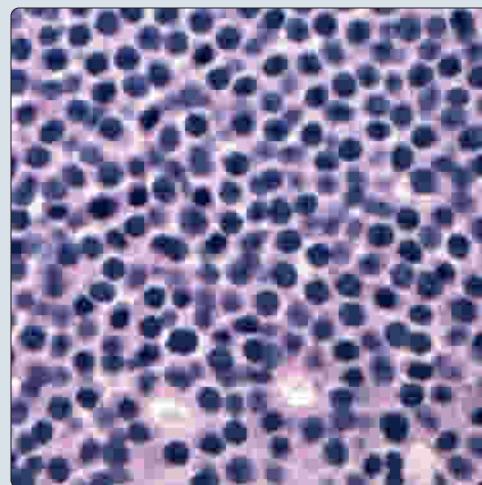


Typical Carcinoid, Uniform Cells



(Left) At high magnification, the cytomorphic features of typical carcinoid include uniform round to oval nuclei with dispersed (salt and pepper) nuclear chromatin and absence of pleomorphism, mitotic activity, and necrosis. (Right) Irrespective of the growth pattern as evident in this diffuse/solid sheet of tumor, the cytomorphic features of typical carcinoid remain unchanged and include cells with bland-appearing round to oval nuclei, dispersed nuclear chromatin, and absence of pleomorphism and mitotic activity.

Typical Carcinoid, Uniform Cells



TERMINOLOGY

Abbreviations

- Neuroendocrine carcinoma (NEC)

Synonyms

- Classification of (laryngeal) neuroendocrine carcinomas of head and neck includes
 - Typical carcinoid or well-differentiated neuroendocrine carcinoma (WDNEC)
 - Atypical carcinoid or moderately differentiated neuroendocrine carcinoma (MDNEC)
 - Small cell carcinoma or poorly differentiated neuroendocrine carcinoma (PDNEC)
 - Small cell undifferentiated neuroendocrine carcinoma (SCUNC); "oat" cell carcinoma
 - Large cell neuroendocrine carcinoma (LCNEC)
 - Subsumed within broader category of PDNEC

Definitions

- Heterogeneous group of malignant neoplasms characterized by presence of epithelial and neuroendocrine differentiation with prognosis predicated on tumor type

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Atypical carcinoid, small cell carcinoma and large cell NEC
 - History of cigarette smoking
- Typical carcinoid
 - Generally not associated with smoking history

CLINICAL ISSUES

Epidemiology

- Incidence
 - In general, NECs are uncommon in head and neck
 - May be identified in virtually all sites of head and neck
 - More common sites include larynx > sinonasal cavity, salivary glands
- Age
 - Generally in 6th and 7th decades of life
- Sex
 - Male > female

Site

- Larynx is most common site of occurrence
 - Supraglottic larynx most common single site of occurrence; glottis and subglottis occasionally
- Frequency of tumor type in larynx: Atypical carcinoid > small cell carcinoma > LCNEC > typical carcinoid

Presentation

- Hoarseness is most common complaint
- Paraneoplastic syndrome
 - Rarely occurs in association with carcinoid tumor and atypical carcinoid
 - Occurs when carcinoid tumor secretes certain chemicals into bloodstream causing variety of signs and symptoms

Treatment

- Surgical approaches
 - **Typical carcinoid**

- Conservative complete resection
- Neck dissection not indicated given low incidence of nodal metastasis at presentation
- **Atypical carcinoid**
 - Depending on site of occurrence, surgery may include partial or total laryngectomy
 - High incidence of cervical node metastasis necessitates neck dissection even in clinically N0 necks
- Adjuvant therapy
 - For small cell carcinoma and LCNEC, primary mode of therapy includes chemoradiotherapy
 - Many patients have disseminated disease at presentation obviating option of laryngectomy and neck dissection

Prognosis

- **Typical carcinoid (WDNEC)**
 - Indolent biology with excellent behavior generally cured following surgical resection
 - 5-year disease-specific survival (DSS) of 100% reported
 - May metastasize in approximately 1/3 of patients
 - Metastases may occur late in disease course to liver and bone
- **Atypical carcinoid tumor (MDNEC)**
 - Prognosis is dependent on extent of disease at presentation
 - Tumor confined to larynx 62% tumor-free over median of 3.9 years
 - Overall 5-year survival: 48%
 - Overall 10-year survival: 30%
 - 5-year DSS of 53%
 - Patients treated with surgery better DSS than those treated with radiotherapy
 - Postoperative radiotherapy does not result in better DSS
 - Fully malignant tumor that often metastasizes to
 - Cervical lymph nodes (43% of patients)
 - Lungs, bone, liver (44% of patients)
 - Skin and subcutaneous tissue (22% of patients)
 - Death results from metastatic disease
 - Prognosis is dependent on extent of disease at presentation
 - When tumor is confined to larynx, 62% tumor free over median of 3 years 9 months
 - Presence of metastatic disease (either at presentation or developing subsequently) is ominous sign with death at intervals ranging from 1-6 years
- **Small cell carcinoma**
 - Highly lethal tumors with aggressive malignant behavior
 - Metastases are common
 - Regional lymph nodes in majority of patients (60-90%); may include liver, lung, bone, and brain
 - Poor
 - 2-year survival: 16%
 - 5-year survival: 5%
 - 5-year DSS of 19%
- **Large cell neuroendocrine carcinoma**
 - Commonly presents with advanced stage (stages III and IV)
 - May be metastatic to cervical lymph nodes at presentation

- May be metastatic to distant sites (e.g., liver) at presentation
- 5-year DSS of 15-21%

MACROSCOPIC

General Features

- For all laryngeal NECs
 - Submucosal nodular or polypoid mass with tan-white appearance
 - Varies in size from a few mm up to 3 cm in diameter
 - ± (typical carcinoid) surface ulceration

MICROSCOPIC

Histologic Features

- **Typical carcinoid**
 - Submucosal tumor arranged in organoid, trabecular, ribbons, or solid growth pattern with fibrovascular stroma
 - Uniform cells, centrally located round nuclei, vesicular chromatin, and eosinophilic cytoplasm
 - Low nuclear to cytoplasmic ratio
 - Stippled (salt and pepper) nuclear chromatin pattern
 - Absence of pleomorphism, mitoses, necrosis
 - Glands &/or squamous differentiation can be seen
 - Surface ulceration uncommon
 - Vascular, lymphatic, and perineural invasion absent
- **Atypical carcinoid**
 - Submucosal tumor in organoid, trabecular, ribbons, cribriform, or solid growth pattern with prominent fibrovascular stroma
 - Infiltrative growth when present may include neurotropism and lymphovascular invasion
 - Hypercellular with mild to marked nuclear pleomorphism, round to oval nuclei, stippled to vesicular chromatin, and eosinophilic to clear to oncocytic cytoplasm
 - Nuclei can be centrally or eccentrically (plasmacytoid) located
 - Nucleoli may be prominent
 - Mitoses uncommon but can be seen, including atypical forms
 - Necrosis may be focally identified
 - Glands, squamous differentiation, and neural-type rosettes can be identified
 - Surface ulceration may be prominent
- **Small cell carcinoma**
 - Submucosal tumor arranged in solid nests, sheets, or ribbons with absence of fibrovascular stromal component
 - Hypercellular with hyperchromatic, pleomorphic, oval to spindle-shaped nuclei, increased nuclear to cytoplasmic ratio, nondescript cytoplasm, and indistinct cell borders
 - Stippled (salt and pepper) nuclear chromatin with absent to inconspicuous nucleoli
 - Crush artifact frequent
 - Abundant mitoses, including atypical forms
 - Confluent foci of necrosis and individual cell necrosis common
 - Nuclear molding identified

- Glands, squamous differentiation, and neural-type rosettes can be identified
- May occur in association with squamous cell carcinoma and less often with adenocarcinoma
 - Referred to as combined or composite tumors
- Surface ulceration present
- Neurotropism and lymphovascular invasion common
- **Large cell neuroendocrine carcinoma**
 - Criteria for diagnosis include (all 4 of requisite criteria must be present to make diagnosis)
 - Presence of features of neuroendocrine differentiation including organoid nesting, trabecular growth, rosettes, and peripheral palisading
 - Presence of enlarged tumor cells with vesicular chromatin, small to prominent nucleoli and moderate to abundant cytoplasm
 - Increase mitotic activity (> 10 mitoses per 10 HPF [2 mm²])
 - Confirmation of neuroendocrine differentiation using immunohistochemical staining for chromogranin, synaptophysin, neuron-specific enolase &/or neural cell adhesion molecule (CD56)

ANCILLARY TESTS

Immunohistochemistry

- Cytokeratins (AE1/AE3, CAM5.2, OSCAR), epithelial membrane antigen **positive**
 - Punctate paranuclear staining may be present (arguably best seen with CAM5.2)
 - High molecular weight cytokeratins, including CK5/6 and CK903 (34βE12) typically **negative** but may be **positive**; when **positive** tends to be focal
 - CK7, CK20 may be **positive**
- Neuroendocrine markers (chromogranin, synaptophysin, CD56, CD57) and NSE **positive**
 - Chromogranin may be **positive** but only focally and may be **negative**; TTF-1, Leu 7, neurofilament protein may be **positive**
- Variability of p63 staining that may include focal to diffuse reactivity
- Calcitonin immunoreactivity is present in atypical carcinoid (primary and metastatic) in > 80%
- Increase proliferation rates by Ki67 (MIB1) staining
 - For atypical carcinoid, usually < 10% and sometimes 10-20% but not > 20%
 - For PDNEC in particular large cell type > 20%
- p53 overexpression in atypical carcinoid and PDNEC
- In association with laryngeal SCUNC, p16, and HPV16 by PCR reported **positive** in a single case
 - Oropharyngeal small cell carcinomas may be p16 positive with confirmation of HPV DNA by molecular analysis
 - Whether there is any definitive link &/or role of high-risk HPV in pathogenesis remains uncertain
 - Presence of p16 and HPV DNA does not appear to alter dismal prognosis

DIFFERENTIAL DIAGNOSIS

Laryngeal Paraganglioma

- Differential for carcinoid tumor
- Absent cytokeratin immunoreactivity

Pathology of Laryngeal Neuroendocrine Neoplasms

	Laryngeal Paraganglioma	Carcinoid Tumor	Atypical Carcinoid	Small Cell Carcinoma	LCNEC
Histology	Cell nest or zellballen pattern separated by fibrovascular stroma; circumscribed & noninvasive	Submucosal, organoid or trabecular growth, & fibrovascular stroma; typically noninvasive	Submucosal; organoid, trabecular, cribriform or solid growth & fibrovascular stroma; invasive	Submucosal, invasive with solid nests, sheets, or ribbons; absence of fibrovascular stroma	Submucosal, invasive with organoid nesting, trabecular growth; rosettes, and peripheral palisading may be present
	Chief cells are predominant cell type	Neoplastic cells are uniform with salt and pepper nuclear chromatin	Neoplastic cells retain salt and pepper chromatin	Hypercellular tumor with salt and pepper nuclear chromatin; crush artifact frequently present	Presence of tumor cells with vesicular chromatin, small to prominent nucleoli and moderate to abundant cytoplasm
	Sustentacular cells lie at periphery of cells nests but are difficult, if not impossible, to identify by light microscopy	Absence of pleomorphism, mitoses, necrosis	Mild to marked nuclear pleomorphism and increased mitotic activity are present; necrosis uncommon; PNI & LVI	Necrosis (confluent foci & individual cell); numerous mitoses, including atypical forms; PNI & LVI	Increased mitotic activity (> 10 mitoses per 10 HPF); necrosis (confluent and individual cell; PNI & LVI)
IHC	Chief cells: CHR, SYN, NSE, NFP positive; sustentacular cells: S100 protein(+); CK(-)	Positive for CK, CHR, SYN, CD56, CD57, NSE, EMA, CEA, TTF-1; may be positive for calcitonin, serotonin, somatostatin, bombesin	Positive for CK, CHR, SYN, CD56, CD57, calcitonin (> 80%); also positive for NSE, NFP, EMA, CEA, TTF-1	Positive CK, CHR, SYN, CD56, CD57; also positive for NSE, NFP, EMA, CEA, TTF-1; calcitonin rarely is positive	Neuroendocrine markers positive (e.g., synaptophysin, others); positive for cytokeratin (AE1/AE3) but CK5/6 and 34βE12 typically negative; calcitonin and TTF-1 negative

IHC = immunohistochemistry; CEA = carcinoembryonic antigen; CHR = chromogranin; CK = cytokeratins; EMA = epithelial membrane antigen; LCNEC = large cell neuroendocrine carcinoma; LVI = lymph-vascular invasion; NFP = neurofibrillary protein; NSE = neuron-specific enolase; PNI = perineural invasion; SYN = synaptophysin; TTF-1 = thyroid transcription factor 1.

- Characteristic S100 protein immunoreactivity along periphery of cell nests (sustentacular cell-like pattern)
- GATA3 immunoreactivity seen in paragangliomas but absent in laryngeal neuroendocrine carcinomas

Medullary Thyroid Carcinoma (MTC)

- Differential for atypical carcinoid
- Overlapping light microscopic and immunohistochemical including calcitonin with atypical carcinoid
 - Serum calcitonin levels almost invariably elevated in MTC and almost always within normal limits in atypical carcinoid

Basaloid Squamous Cell Carcinoma

- Differential for atypical carcinoid, PDNEC
- Cytokeratin staining present but lacks punctate paranuclear staining seen in NEC
- High molecular weight keratins including CK5/6 and CK903 (34βE12), and p63 diffusely and strongly **positive**
 - NECs typically lack such diffuse and strong staining

Malignant Melanoma


- Presence of S100 protein and melanocytic immunomarkers
- Absent cytokeratins and neuroendocrine markers

Malignant Lymphoma

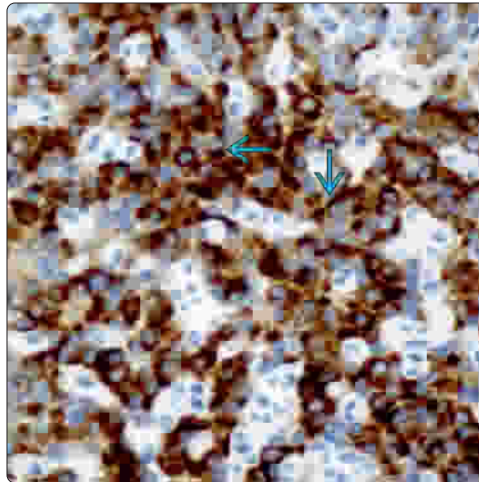
- Presence of hematolymphoid immunomarkers
- Absent cytokeratins and neuroendocrine markers

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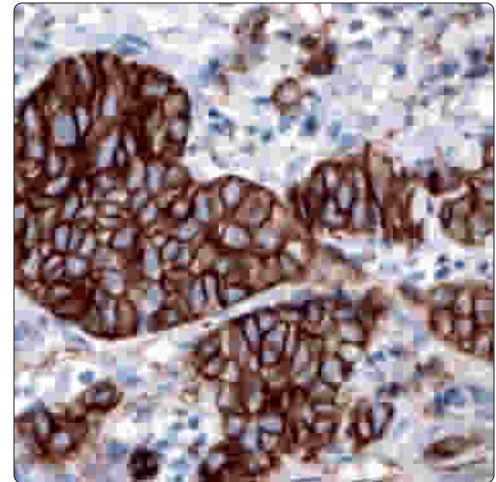
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(Left) The lesional cells of typical carcinoid, like other neuroendocrine carcinomas, show strong immunoreactivity for cytokeratins, including CAM5.2 with characteristic paranuclear punctate (dot-like) staining . **(Right)** In addition to epithelial markers, typical carcinoids also show variable immunoreactivity for neuroendocrine markers that may include diffuse staining for chromogranin.

Typical Carcinoid, Cytokeratin Staining

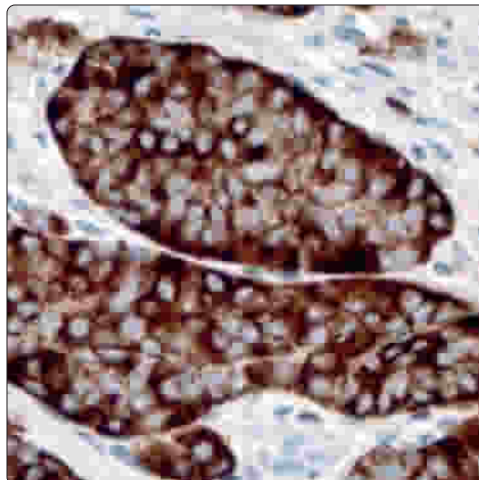


Typical Carcinoid, Chromogranin Staining

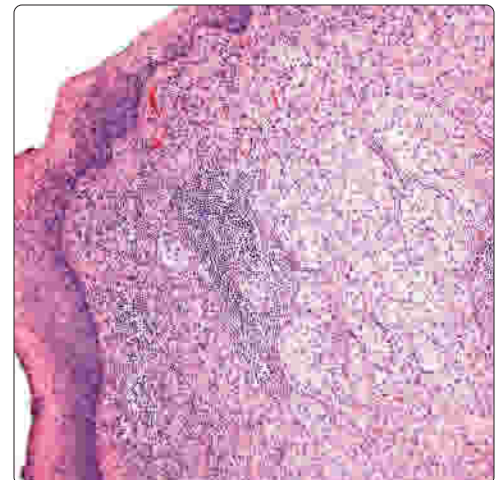


(Left) Lesional cells are diffusely immunoreactive for synaptophysin. Light microscopic features, including the character of nuclear chromatin pattern, absence of significant pleomorphism & mitotic activity, coupled with the presence of immunostaining for epithelial markers & neuroendocrine markers, is diagnostic for a neuroendocrine neoplasm, specifically typical carcinoid. **(Right)** Atypical carcinoid appears as a submucosal cellular infiltrate with organoid (cell nest) growth and fibrovascular stroma.

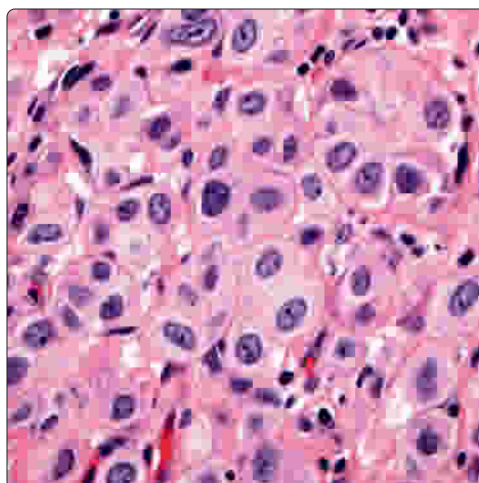
Typical Carcinoid, Synaptophysin Staining



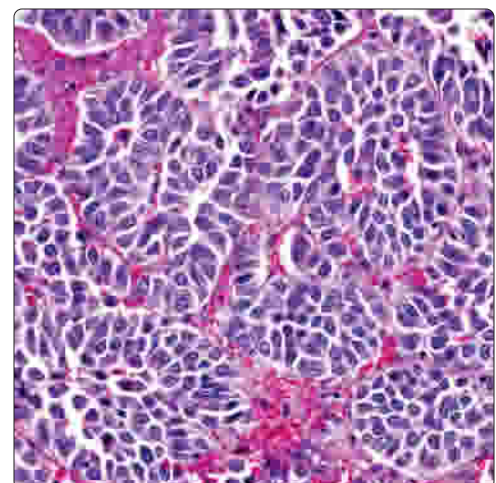
Atypical Carcinoid, Organoid Growth



Atypical Carcinoid, Cell Nests and Nuclear Pleomorphism

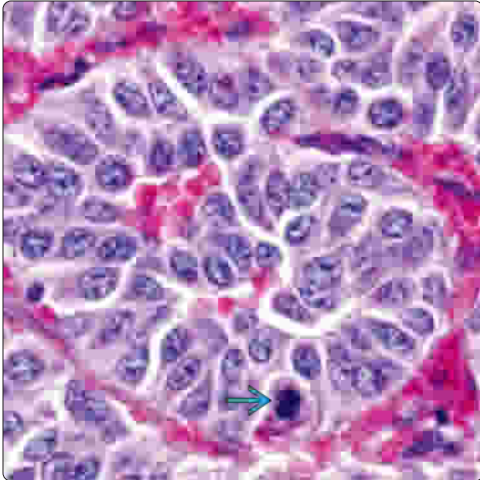


Atypical Carcinoid, Cell Nests and Nuclear Pleomorphism

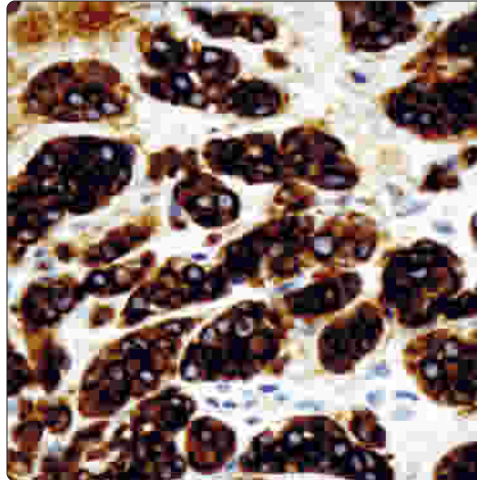



(Left) At higher magnification, the cell nest pattern is composed of cells with round to oval nuclei, dispersed (salt and pepper) nuclear chromatin, inconspicuous to small nucleoli and eosinophilic cytoplasm; variable but identifiable nuclear pleomorphism is present. Although mitoses are not present, the degree of nuclear pleomorphism is greater than in typical carcinoid. **(Right)** Another example of an atypical carcinoid shows solid to organoid (cell nest) growth with fibrovascular stroma.

Atypical Carcinoid, Mitotic Activity

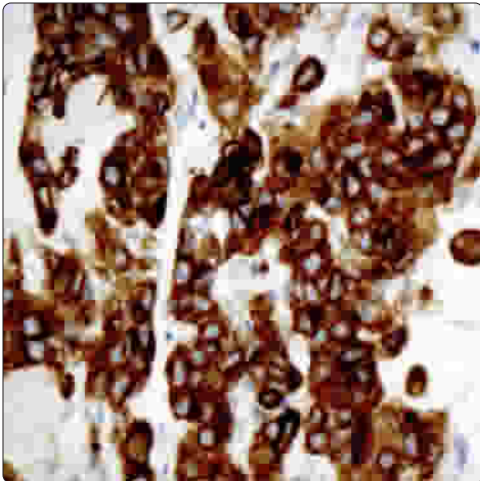


Atypical Carcinoid, Cytokeratin Reactivity

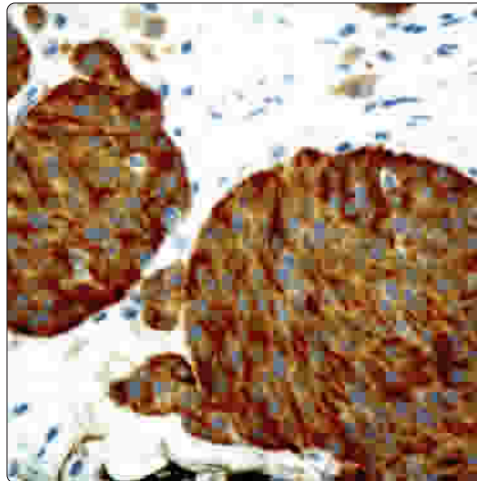


(Left) Cell nest composed of cells with round to oval nuclei, dispersed (salt and pepper) nuclear chromatin, inconspicuous to small nucleoli, and basophilic to eosinophilic cytoplasm is shown. Nuclear pleomorphism is present, and there is a mitotic figure . The greater nuclear pleomorphism and presence of mitotic figures separates atypical carcinoid from typical carcinoid. (Right) Diffuse and strong cytokeratin (CAM5.2) staining is a finding seen in all neuroendocrine carcinomas, including atypical carcinoids.

Atypical Carcinoid, Synaptophysin Reactivity

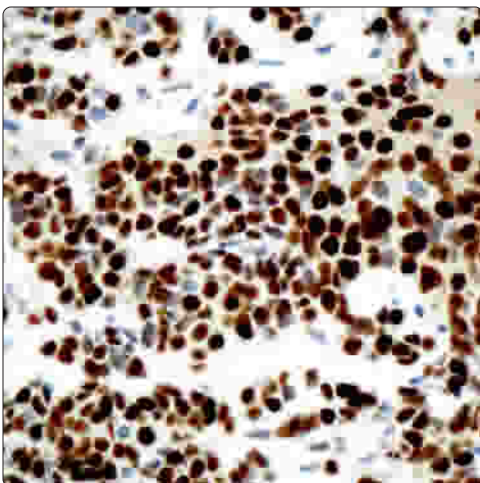


Atypical Carcinoid, Calcitonin Reactivity

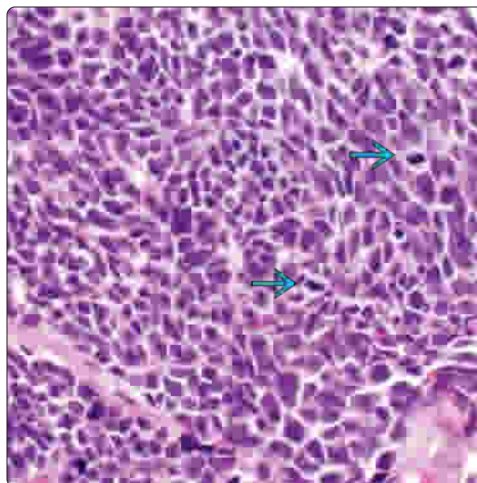



(Left) Atypical carcinoid shows immunoreactivity for synaptophysin. Similar to carcinoid tumors, the combination of the light microscopic features, including dispersed chromatin coupled with the presence of immunoreactivity for cytokeratins and neuroendocrine markers, points to a diagnosis of a neuroendocrine carcinoma. (Right) Immunoreactivity for calcitonin can be seen in a majority of atypical carcinoids but in contrast to medullary carcinoma, serum calcitonin levels are not elevated.

Atypical Carcinoid, TTF-1 Reactivity




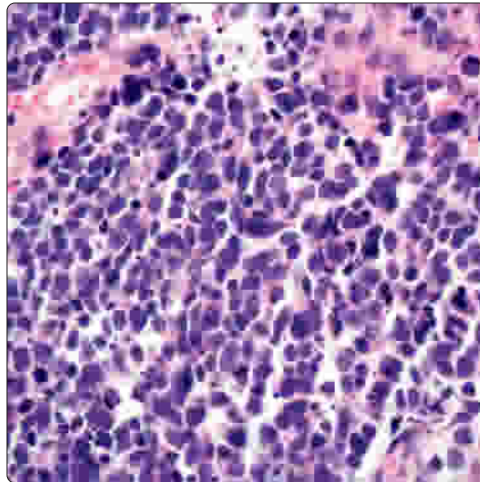
Small Cell Carcinoma, Solid Growth



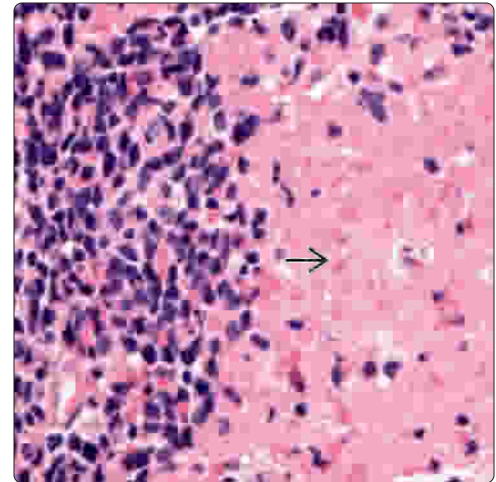
(Left) In addition to cytokeratins, neuroendocrine markers, and calcitonin, neuroendocrine carcinomas may be variably reactive for TTF-1 characterized by nuclear staining. (Right) Laryngeal small cell carcinoma is characterized by a hypercellular proliferation with solid growth composed of hyperchromatic nuclei with dispersed (salt and pepper) nuclear chromatin, nuclear molding, inconspicuous nucleoli, and increased mitotic activity .

Small Cell Carcinoma, Individual Cell Necrosis


(Left) At higher magnification, the hypercellular proliferation includes cells with dispersed (salt and pepper) nuclear chromatin, inconspicuous nucleoli, and increased mitotic activity. Nuclear molding and individual cell necrosis are present. **(Right)** Necrosis may vary from case to case and even within the same case of small cell carcinoma. In this example, a confluent area of necrosis  is seen adjacent to viable lesional cells, the latter showing characteristic features of a small cell carcinoma.

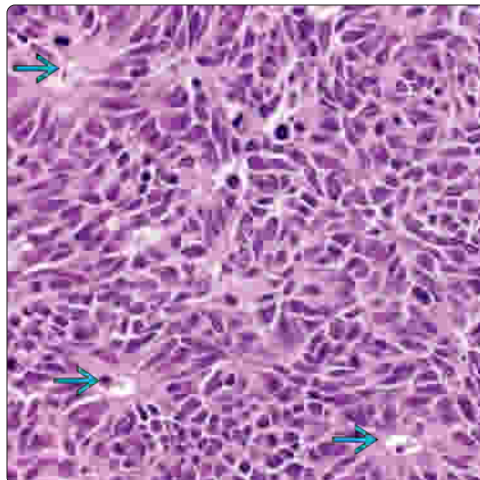


Small Cell Carcinoma, Confluent Necrosis

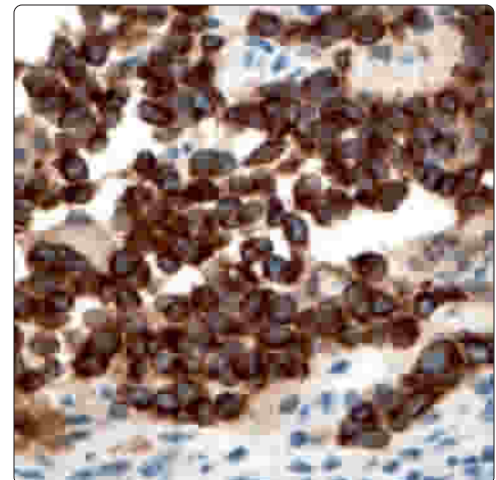


Small Cell Carcinoma, Rosettes

(Left) In this example of a laryngeal small cell carcinoma, neural-type rosettes  are present. Rosettes are not unique to neuroendocrine carcinomas and can be seen in other tumor types, including (but not limited to) olfactory neuroblastoma and basaloid squamous cell carcinoma. **(Right)** Repeating the theme associated with neuroendocrine carcinomas, diffuse immunoreactivity is present in small cell carcinomas for cytokeratins, including CAM5.2.

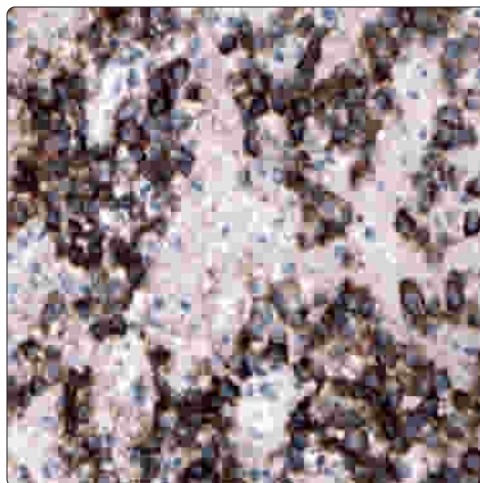


Small Cell Carcinoma, Cytokeratin Reactivity

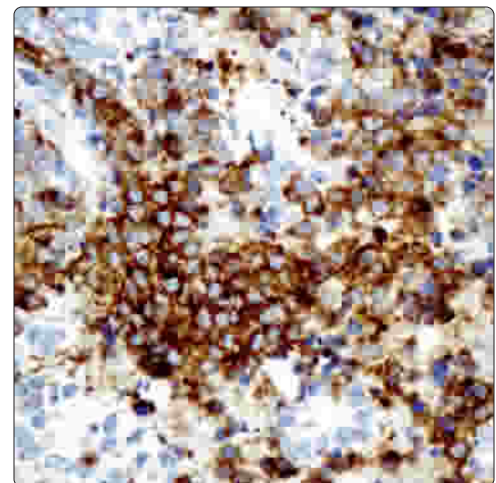


Small Cell Carcinoma, Chromogranin Reactivity

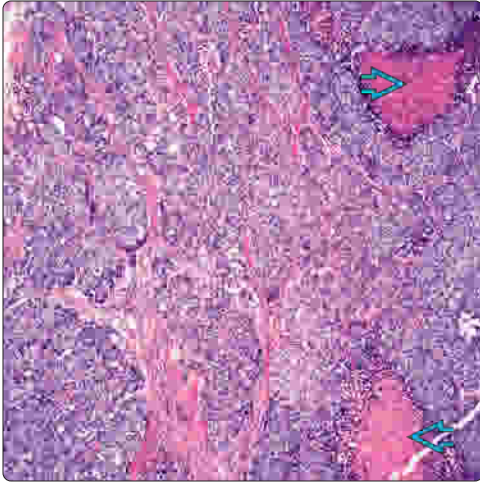
(Left) Immunoreactivity is present for chromogranin but often is focal and less diffusely reactive in comparison to synaptophysin. **(Right)** Immunoreactivity is present for synaptophysin. Similar to the typical and atypical carcinoids, the combination of the light microscopic features and immunoreactivity for epithelial and neuroendocrine markers assist in the diagnosis. The nuclear pleomorphism, increased mitotic activity, and necrosis differentiates small cell carcinoma from typical carcinoid and atypical carcinoid.



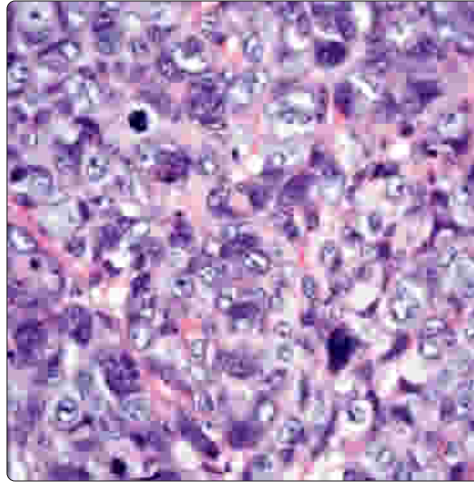
Small Cell Carcinoma, Synaptophysin Reactivity



Large Cell Neuroendocrine Carcinoma, Growth Patterns

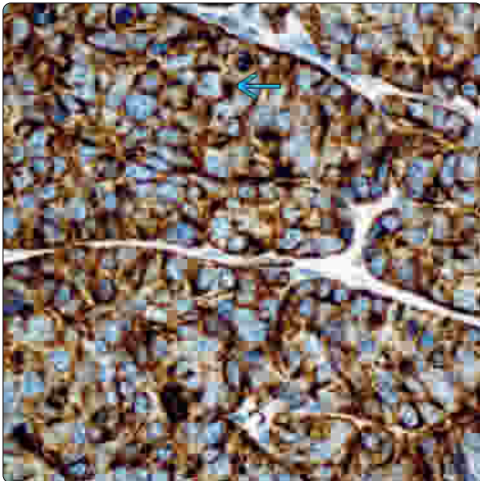


Large Cell Neuroendocrine Carcinoma, Cytomorphology

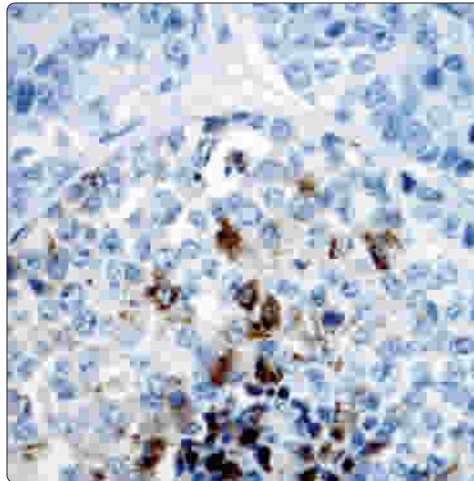


(Left) The histologic findings seen in large cell neuroendocrine carcinoma include the presence of features of neuroendocrine differentiation characterized by organoid, cell nest &/or trabecular growth. Foci of comedo-type necrosis are present. **(Right)** In addition to the growth patterns, the presence of large cells with vesicular chromatin, identifiable nucleoli, moderate to abundant cytoplasm, plus increased mitotic activity (i.e., > 10 mitoses per 10 HPF) are requisite features in the diagnosis.

Large Cell Neuroendocrine Carcinoma, Cytokeratin Reactivity

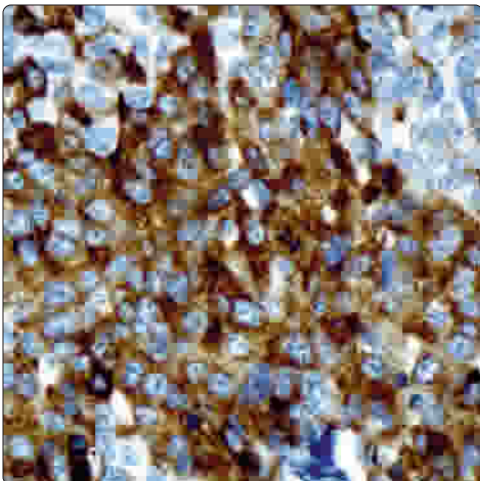


Large Cell Neuroendocrine Carcinoma, Chromogranin Reactivity

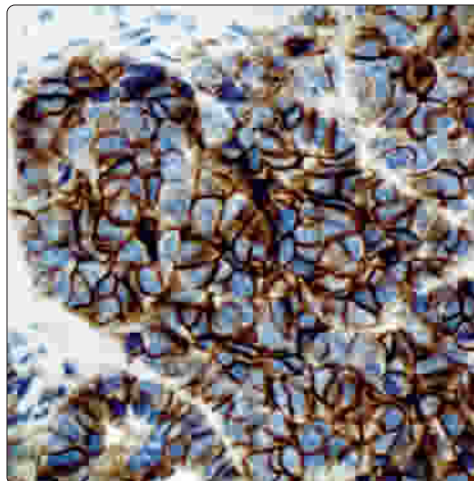


(Left) Consistent immunoreactivity for cytokeratins, including CAM5.2 with paranuclear punctate (dot-like) staining is a finding in all neuroendocrine carcinomas, including the large cell type. **(Right)** Immunoreactivity is present for chromogranin but, as seen in small cell carcinoma, tends to be focal and less diffusely reactive in comparison to synaptophysin.

Large Cell Neuroendocrine Carcinoma, Synaptophysin Reactivity



Large Cell Neuroendocrine Carcinoma, CD56 Reactivity



(Left) Confirmation of neuroendocrine differentiation by immunohistochemical staining also includes synaptophysin. **(Right)** In addition, CD56 (membranous staining pattern), while not limited or unique to neuroendocrine carcinomas, adds additional support to the diagnosis of large cell neuroendocrine carcinoma. Requisite features in the diagnosis include growth patterns, cytomorphology, increased mitotic activity, and immunoreactivity for neuroendocrine markers.

KEY FACTS

ETIOLOGY/PATHOGENESIS

- Disordered ossification of laryngeal cartilages at points of mechanical stress/tension (muscle insertion points)

CLINICAL ISSUES

- Cricoid cartilage (85%)
- Does not develop in elastic cartilages (i.e., epiglottis)
- Male >> female (4:1)
- Mean: 60-65 years
- Conservative, laryngeal-function preserving surgery
- Grade does not alter prognosis
- Metastatic disease is vanishingly rare

IMAGING

- Fine, punctate stippled to coarse (popcorn) calcifications within mass

MACROSCOPIC

- Inner, posterior lamina (midline) of cricoid cartilage most commonly affected

MICROSCOPIC

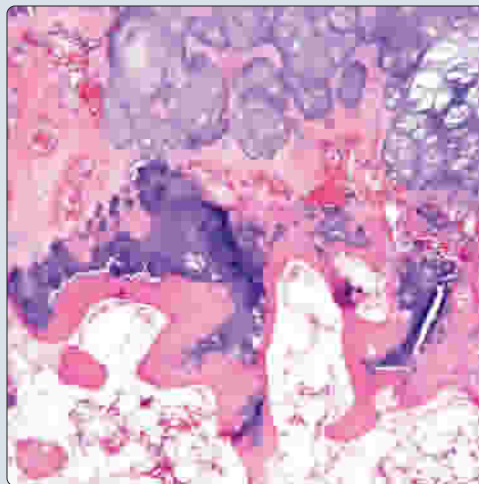
- Bone invasion and destruction
- Increased cellularity in comparison to normal cartilage
- Loss of normal architecture and lacunar distribution (cluster disarray)
- Tumors separated into 3 grades
- 3 tumor subtypes: Myxoid, mesenchymal, dedifferentiated

TOP DIFFERENTIAL DIAGNOSES

- Chondroma
- Spindle cell (sarcomatoid) squamous cell carcinoma

Bone Destruction by Neoplastic Cartilage

(Left) H&E shows neoplastic cartilage in the upper field infiltrating bone and native cartilage. There is cluster disarray. (Right) H&E shows normal cartilage immediately juxtaposed to the increased cellularity of low-grade chondrosarcoma. A difference in cell size and lacunar distribution is noted.

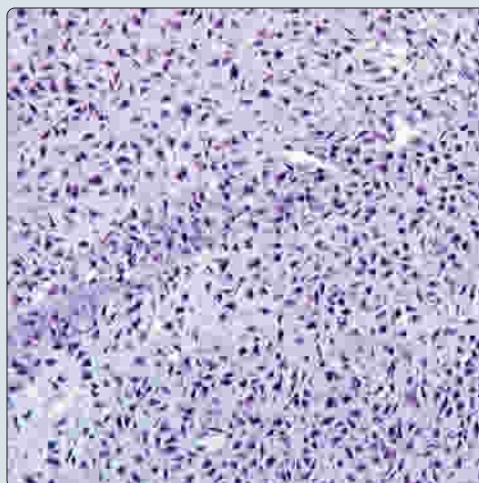


Normal and Neoplastic Cartilage

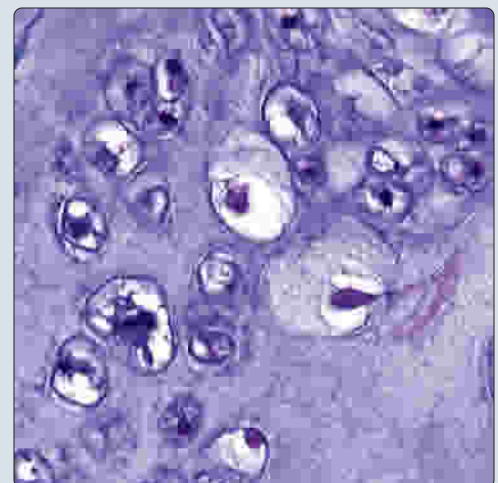


High-Grade Chondrosarcoma With High Cellularity

(Left) H&E shows remarkably increased cellularity and lacunar space disorganization in this grade III chondrosarcoma. (Right) H&E shows atypical nuclei within enlarged lacunar spaces in this grade I chondrosarcoma.



Irregular Lacunar Space and Atypical Nuclei



TERMINOLOGY

Definitions

- Malignant cartilage forming neoplasm

ETIOLOGY/PATHOGENESIS

Disordered Ossification

- Ossification of laryngeal hyaline cartilages at points of mechanical stress/tension (muscle insertion points)

Ischemic Change

- Ischemic change in chondromas related to mechanical trauma predisposes to malignant transformation

Continuum With Chondroma

- Chondroma develop a decade earlier, suggesting continuum

CLINICAL ISSUES

Epidemiology

- Incidence
 - 1% of all laryngeal malignancies; 75% of sarcomas
- Age
 - Mean: 60-65 years; range: 25-91 years
- Sex
 - Male > > female (4:1)

Site

- Cricoid cartilage (85%)
- Does **not** develop in elastic cartilages (i.e., epiglottis)

Presentation

- Difficulty breathing due to progressive narrowing by endolaryngeal growth
- Hoarseness, dyspnea, dysphagia, stridor
- Mass for thyroid cartilage neoplasms specifically
- Symptoms present for long duration (> 2 years)

Treatment

- Requires long-term follow-up, often with repeated "limited" surgeries to maintain function
- Complete but conservative laryngeal function-preserving surgery
 - Multiple surgeries over many years for recurrences
 - Voice-preserving surgeries give best long-term quality of life (tracheal autotransplantation; rib interposition)

Prognosis

- Excellent (> 95% 10-year survival)
- Recurrences develop in up to 40% of patients, but metastatic disease is rare
- Tumor grade does not alter prognosis
- Histologic subtype does not change outcome, but myxoid tumors may be more likely to recur

IMAGING

General Features

- Ill-defined, invasive, destructive, hypodense mass
- Fine, punctate to coarse (popcorn) calcifications

MACROSCOPIC

General Features

- Inner, posterior, midline lamina of cricoid
- Crunchy, hard, lobular mass
- Glistening, blue-gray, semitranslucent myxoid-mucoid cut surface
- Dedifferentiated tumors have fleshy areas
- Mean size: 3.5 cm; range: Up to 12 cm

MICROSCOPIC

Histologic Features

- Bone invasion and destruction
- Basophilic cartilaginous matrix in comparison to eosinophilic normal cartilage
- Cellular tumors with loss of normal architecture and lacunar distribution (cluster disarray)
- Nuclear atypia with bi- and multinucleation of cells with increased nuclear to cytoplasmic ratio
- Ischemic change (blue, granular cytoplasm) can be seen in background
- Mitotic figures and necrosis rarely present (only in high-grade tumors)
- Tumors separated into 3 grades
- 3 tumor subtypes
 - Myxoid chondrosarcoma (grade II)
 - Mesenchymal chondrosarcoma (grade III)
 - Dedifferentiated chondrosarcoma (grade III)

DIFFERENTIAL DIAGNOSIS

Chondroma

- Small lesion (< 2 cm), very uncommon, showing slightly increased cellularity over normal

Spindle Cell Sarcomatoid Squamous Cell Carcinoma

- Metaplastic/malignant cartilage may develop, but tumor is polypoid, associated with spindle cell proliferation
- Keratin immunoreactive in 70% of cases

Chondrometaplasia

- Multifocal elastic cartilage nodules within vocal cord, blending with surrounding tissue (no mass)

GRADING

Grade 1 (Low)

- Mildly increased cellularity, mild pleomorphism

Grade 2 (Intermediate)

- Moderate cellularity and pleomorphism, ↓ cartilage matrix



Grade 3 (High)

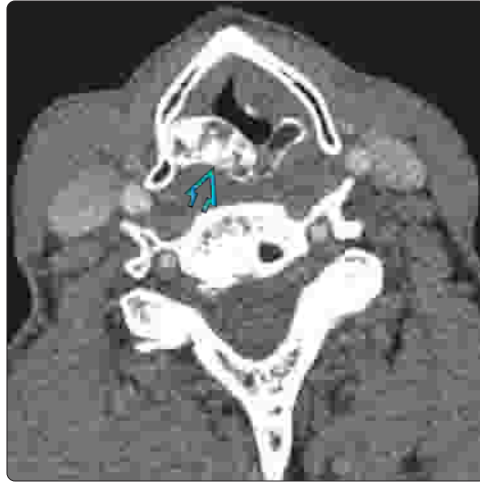
- High cellularity, marked pleomorphism, ↑ mitoses, necrosis

SELECTED REFERENCES

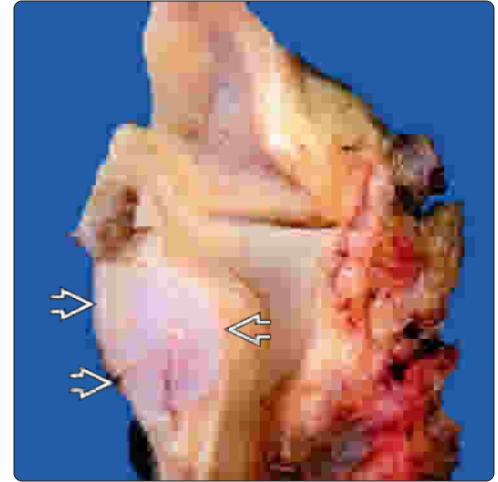
1. Purohit BS et al: Dedifferentiated laryngeal chondrosarcoma: combined morphologic and functional imaging with positron-emission tomography/magnetic resonance imaging. *Laryngoscope*. 124(7):E274-7, 2014
2. Thompson LD et al: Chondrosarcoma of the larynx: a clinicopathologic study of 111 cases with a review of the literature. *Am J Surg Pathol*. 26(7):836-51, 2002

CT of Cricoid Mass With Popcorn Calcifications


(Left) Radiologic image shows destruction of the posterior lamina of the cricoid cartilage by a neoplastic proliferation. Note the fine, punctate to coarse (popcorn) calcifications . (Right) Gross photograph shows a translucent, bluish neoplastic proliferation within the posterior cricoid cartilage , which proved to be a chondrosarcoma.

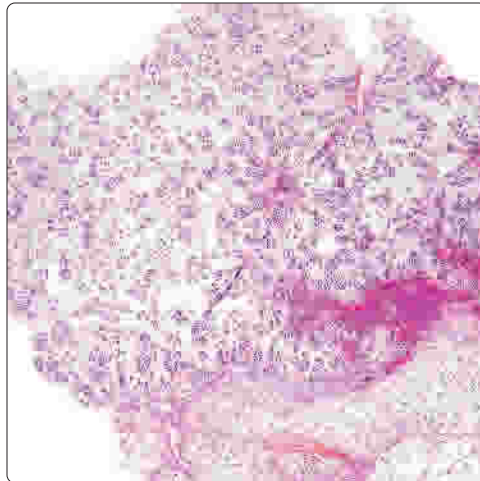


Cricoid Cartilage Expanded by Neoplasm

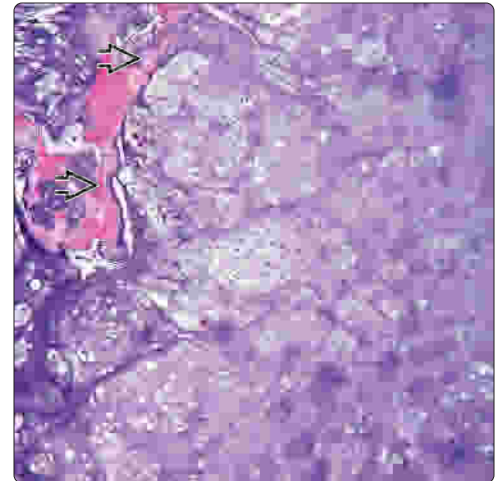


Cluster Disarray in Chondrosarcoma


(Left) H&E shows a highly cellular neoplastic cartilaginous neoplasm. There is cluster disarray or disorganization. (Right) H&E shows an increased cellularity within a cartilaginous neoplasm that destroys bone  in this grade I chondrosarcoma.

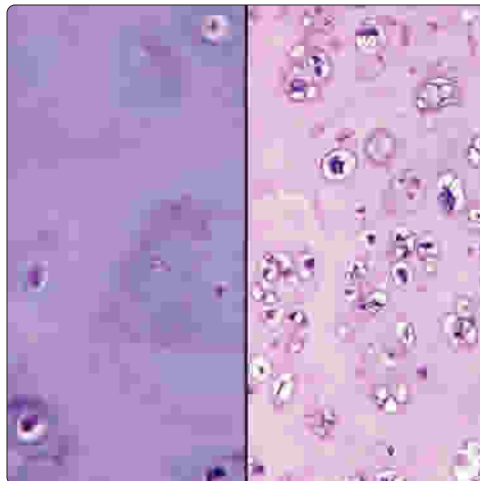


Cartilage Destroying Bone

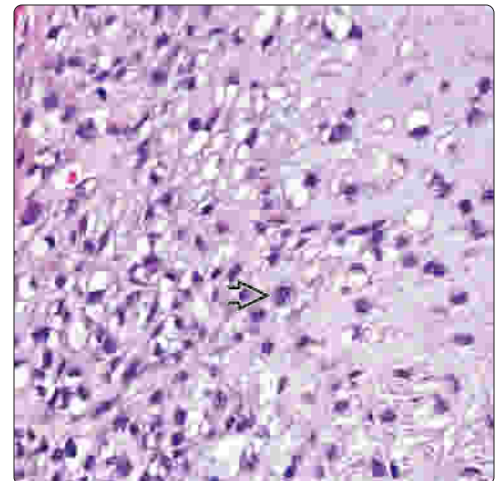


Normal and Neoplastic Cartilage (Same Magnification)

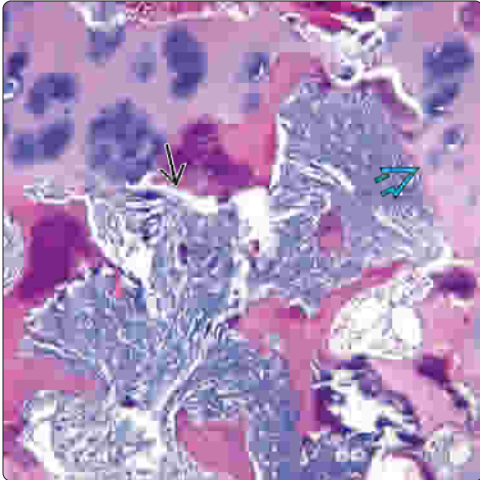
(Left) H&E shows normal cartilage (left) with neoplastic cartilage (right) taken at the same magnification. This shows an increased number of lacunar spaces and increased nuclear:cytoplasmic ratio. (Right) H&E shows increased cellularity and a single mitotic figure  in this grade II chondrosarcoma. Mitoses and necrosis are infrequently identified in chondrosarcoma.



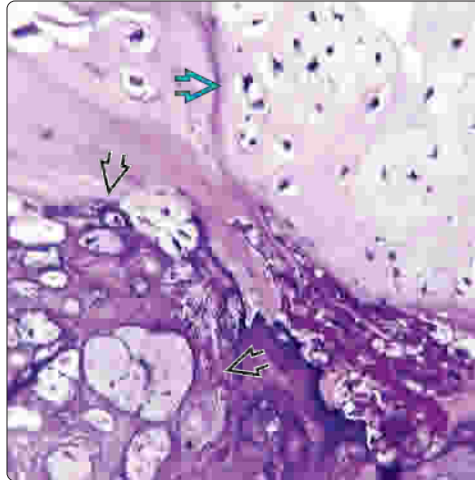
Mitosis in Chondrosarcoma



Chondrosarcoma Invading Bone and Cartilage

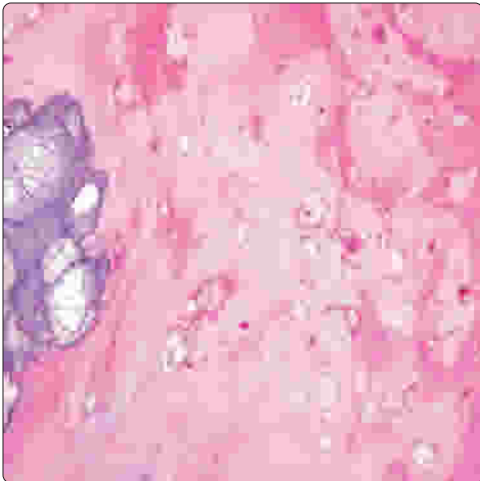


Ischemic Change in Chondroma

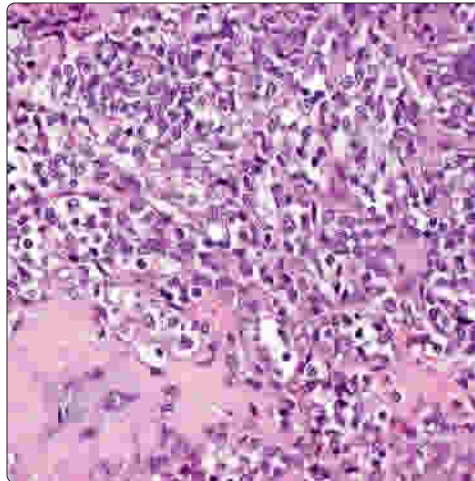


(Left) The neoplastic cartilage is noted to be destroying bone [blue arrow], while also seen expanding into and destroying native cartilage [green arrow]. (Right) H&E shows ischemic change in a chondroma [blue arrow] immediately adjacent to a chondrosarcoma [green arrow]. Ischemia is thought to be etiologic in tumor development.

Tumor Necrosis in Chondrosarcoma

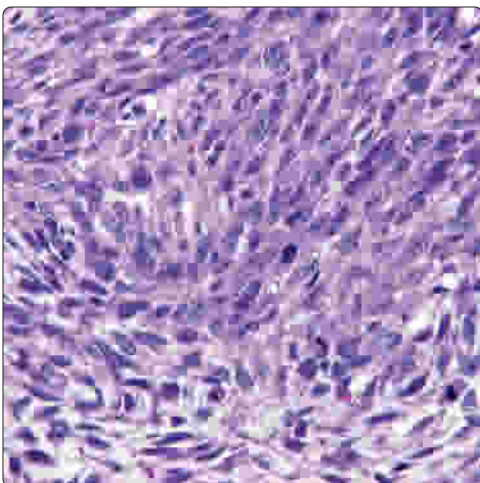


Mesenchymal Chondrosarcoma

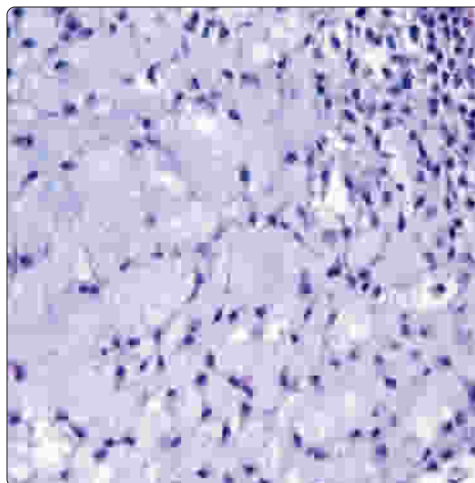


(Left) There is tumor necrosis in this chondrosarcoma, where there is pink change in the cartilage matrix, and a loss of nuclear details. This is different from ischemic change, which shows a bluish cytoplasmic granularity. (Right) H&E shows a "small round blue cell" population with associated cartilage, diagnostic of mesenchymal chondrosarcoma. This is different from dedifferentiated chondrosarcoma, which shows a spindle cell population (sarcoma).

Dedifferentiated Chondrosarcoma



Myxoid Chondrosarcoma



(Left) This dedifferentiated chondrosarcoma shows a spindle cell population (sarcoma) but without cartilage seen in this field. (Right) H&E shows the "string of beads" or "string of pearls" pattern diagnostic for a myxoid chondrosarcoma.

Metastatic/Secondary Tumors

KEY FACTS

TERMINOLOGY

- Tumors that secondarily involve larynx or hypopharynx that originate from, but are not in continuity with, primary malignancies of other sites
 - Lymphomas and leukemias are excluded by definition

CLINICAL ISSUES

- Uncommon (< 0.2% of all malignancies of larynx)
- Older ages, correlated with increased malignancies of other anatomic sites
- Male > female (2:1)
- Supraglottis most common (40%)
 - Multifocal sites within larynx are common
- Prognosis is usually grave

MACROSCOPIC

- Submucosal mass
- Surface epithelium usually intact



MICROSCOPIC

- Specific tumor type dictates histology
- Most common tumors are melanomas or carcinomas
 - Melanoma (40%)
 - Kidney (13%)
 - Breast (9%)
 - Lung (8%)
 - Prostate (7%)
 - Gastrointestinal tract (colon and stomach) (6%)
- Mesenchymal tumors rarely metastasize to larynx

TOP DIFFERENTIAL DIAGNOSES

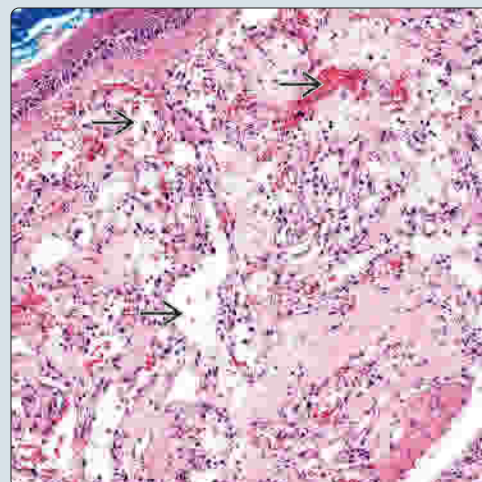
- Primary tumor
 - Primary adenocarcinomas of larynx are rare
- Direct extension
 - Thyroid gland tumors (especially medullary carcinoma)
 - Squamous cell carcinoma of esophagus may extend into larynx

Metastatic Renal Cell carcinoma



(Left) Hematoxylin and eosin reveals a polypoid mass showing ulceration. The neoplastic proliferation is seen filling the stroma of the polyp . This is a metastatic renal cell carcinoma with vascularized stroma. (Right) Hematoxylin and eosin shows an intact squamous mucosa overlying the richly vascularized metastatic clear cell renal cell carcinoma. Note the vascularized neoplastic spaces .

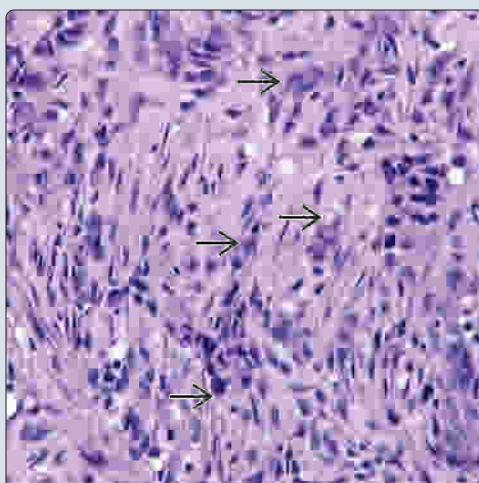


Metastatic Clear Cell Renal Cell Carcinoma

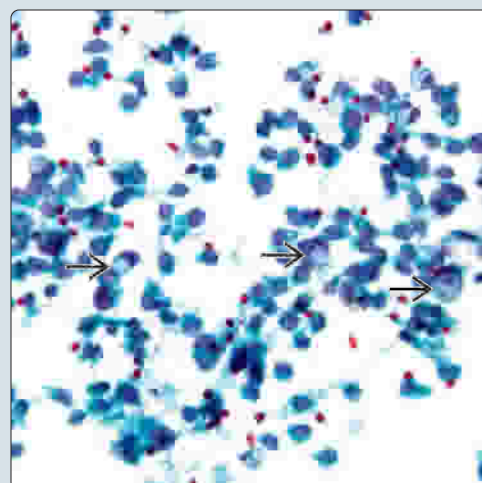


Infiltrating Breast Ductal Carcinoma

(Left) There is an infiltration by neoplastic adenocarcinoma cells in a single file . The primary tumor was identified in the breast. There is a heavy fibroblastic stroma separating the tumor cells. (Right) Papanicolaou stain of a cellular smear shows mucin vacuoles  in the cytoplasm of metastatic breast carcinoma to the larynx.



Fine-Needle Aspiration of Metastatic Breast Carcinoma



TERMINOLOGY**Definitions**

- Tumors secondarily involving larynx or hypopharynx that originate from, but are not in continuity with, primary malignancies of other sites
 - Lymphomas and leukemias are excluded by definition

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Uncommon
 - < 0.2% of all malignancies of larynx
- Age
 - Older ages, correlated with increased malignancies of other anatomic sites
- Sex
 - Male > female (2:1)

Site

- Mucosa-submucosa
 - Supraglottis most common (40%)
 - Subglottis (20%)
 - Glottis (10%)
- Cartilages
 - Usually areas that have undergone endochondral ossification
- Multifocal sites within larynx are common
 - ~ 35% of cases

Presentation

- Hoarseness and voice changes
- Difficulty breathing and stridor

Treatment

- Options, risks, complications
 - Rarely, metastatic disease to larynx may be the only isolated metastasis
 - Most commonly with renal cell carcinoma
- Surgical approaches
 - Excision is performed for symptomatic relief

Prognosis

- Matches underlying disease but usually part of disseminated disease
- Prognosis is usually grave
 - However, renal cell carcinoma may be exception, associated with good prognosis with isolated metastatic foci

MACROSCOPIC**General Features**

- Submucosal mass
- Surface epithelium usually intact

MICROSCOPIC**Histologic Features**

- Specific tumor type dictates histology
- Most common tumors are melanomas or carcinomas
 - Melanoma (40%)

- Kidney (13%)
- Breast (9%)
- Lung (8%)
- Prostate (7%)
- Gastrointestinal tract (colon and stomach) (6%)
- Of carcinomas, adenocarcinomas are most frequent, tumor type that is uncommon as primary larynx tumor
- Mesenchymal tumors rarely metastasize to larynx
 - Leiomyosarcoma is most common of mesenchymal lesions to metastasize

DIFFERENTIAL DIAGNOSIS**Primary Tumor**

- Primary poorly differentiated tumors may need to be separated from metastatic tumors
 - Separation can usually be achieved by history, radiographic studies, and immunohistochemistry
 - Primary adenocarcinomas of larynx are rare
 - Salivary gland tumor-type primaries are more frequent

Direct Extension

- Thyroid gland tumors (especially medullary carcinoma) must be separated from primary and metastatic lesions
 - Frequently radiographic correlation is required, as immunohistochemistry is insufficient
 - Primary atypical carcinoid tumors of larynx are usually calcitonin immunoreactive
 - Serum calcitonin levels usually positive in thyroid gland tumors and negative in primary larynx carcinoma
- Squamous cell carcinoma of esophagus may extend into larynx
- Hematologic neoplasms (lymphoma and plasmacytoma/multiple myeloma) may mimic primary tumors
 - Clinical, radiographic, or laboratory investigation will usually resolve this question

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PRIMARY TUMOR**Specimen**

- Used for biopsies or resection
 - Stripping; laser excision; supraglottic, vertical, partial, or total laryngectomy should be designated
- Supraglottis, glottis, subglottis, or combinations
 - Tumor staging is separated by supraglottis, glottis, and subglottis anatomic sites and subsites
- Laterality: Right, left, bilateral, midline, or transglottic
- Exact tumor site should be stated
- Tumor focality and size (in centimeters)
- Gross tumor descriptor: Polypoid, exophytic, endophytic, ulcerated, sessile

Histologic type

- Squamous cell carcinoma accounts for vast majority, with variants designated as they are recognized
 - Variants: Acantholytic, adenosquamous, basaloid, papillary, exophytic, spindle cell, and verrucous
- Other tumor types recorded as noted
 - Lymphoepithelial carcinoma, giant cell carcinoma, neuroendocrine tumors, salivary gland carcinomas, and mucosal melanoma

Histologic Grade

- Separated into well, moderately, and poorly differentiated

Invasion

- Lymphovascular and perineural invasion
- Margin assessment
 - Distance to closest margin (oriented if possible), in millimeters, for both invasive tumor and moderate dysplasia and higher

REGIONAL LYMPH NODES**Cervical Lymph Nodes: Unilateral or Bilateral**

- Separated into pN0, N1, N2 (a, b, c), and N3 based on number and size of lymph nodes affected
- N1: 1 ipsilateral lymph node < 3 cm

- N2: 1 ipsilateral lymph node > 3 ≤ 6 cm (pN2a) or multiple ipsilateral lymph nodes ≤ 6 cm (pN2b) or in bilateral or contralateral lymph nodes ≤ 6 cm (pN2c)
- N3: Metastases in lymph node > 6 cm

PROGNOSTIC GROUPS**Supraglottis**

- T1: Tumor in 1 subsite with normal vocal cord mobility
- T2: Extension into adjacent subsites (e.g., mucosa of tongue base, vallecula, medial wall of pyriform sinus) without fixation of larynx
- T3: Limited to larynx with vocal cord fixation &/or invasion of postcricoid area, preepiglottic space, paraglottic space, inner cortex of thyroid cartilage
- T4: Separated into T4a (moderately) and T4b (very) based on extent of advanced local disease

Glottis

- T1a: 1 vocal cord; T1b: Both vocal cords
- T2: Supra- &/or subglottis extension &/or impaired vocal cord mobility
- T3: Limited to larynx with vocal cord fixation &/or invasion of paraglottic space &/or inner cortex of thyroid cartilage
- T4: Separated into T4a (moderately) and T4b (very) based on extent of advanced local disease

Subglottis

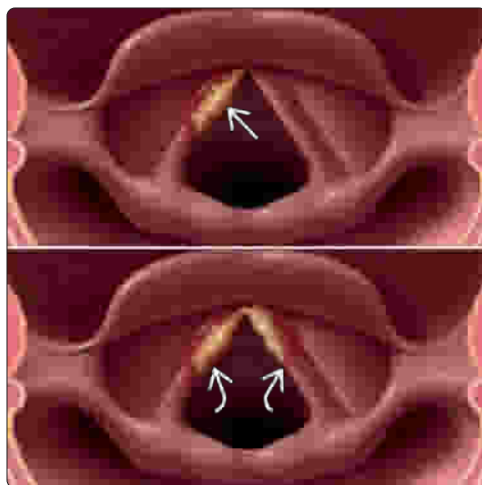
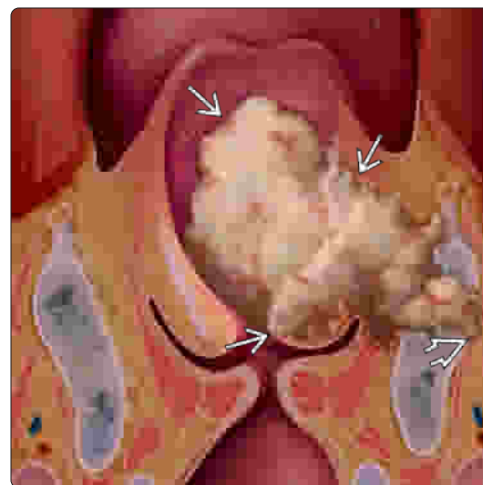
- T1: Limited to subglottis
- T2: Extends to vocal cord(s) with normal or impaired mobility
- T3: Limited to larynx with vocal cord fixation
- T4: Separated into T4a (moderately) and T4b (very) based on extent of advanced local disease

Advanced Local Disease

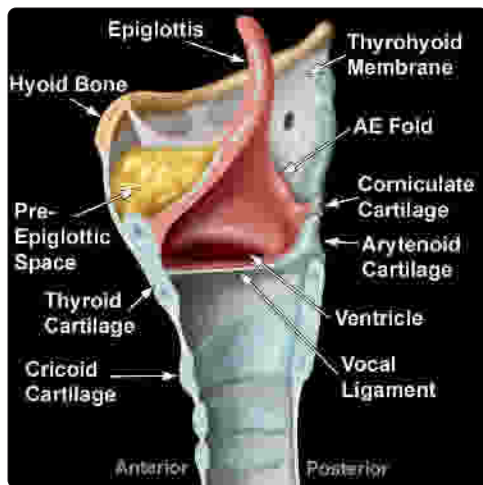
- 4a: Tumor invades through thyroid cartilage &/or invades tissues beyond larynx (e.g., trachea, soft tissues of neck, including deep extrinsic muscle of tongue, strap muscles, thyroid, or esophagus)
- 4b: Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Vocal Cord pT1a and pT1b Tumors

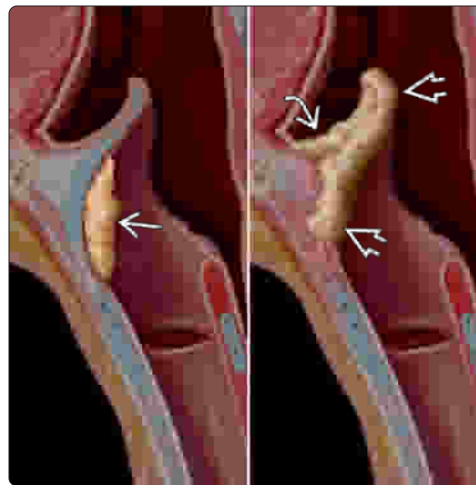
(Left) Graphic depicts endoscopic view of a pT1a glottic tumor confined to 1 vocal cord (top) and a pT1b tumor that involves both vocal cords (bottom). (Right) Coronal graphic shows a pT4a supraglottic squamous cell carcinoma (SCCa) extending laterally from the supraglottis through the paraglottic fat to invade through the left thyroid cartilage. Extension to paralaryngeal tissues, such as trachea, thyroid, esophagus, deep extrinsic muscles of tongue, or strap muscles, would also denote pT4a.

**pT4a Supraglottic Tumor**

Basic Anatomic Landmarks: Sagittal

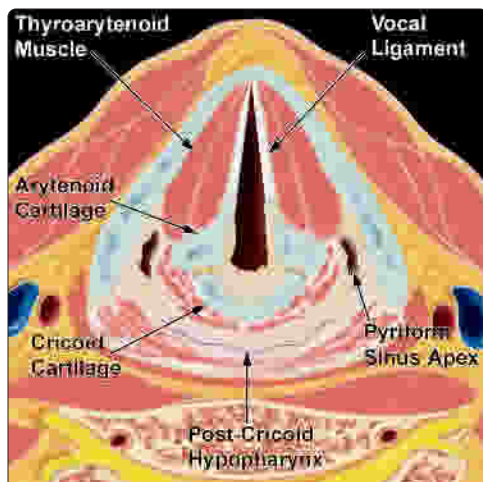


Sagittal Graphic of Supraglottic Tumors

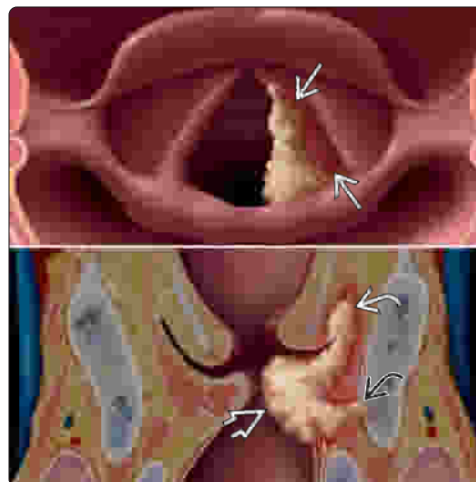


(Left) Basic anatomic landmarks of the larynx are used in accurate classification and separation of specific tumors into location and stage. The vocal cords are used to separate tumors in supraglottic, glottic, and subglottic regions, 1 of the most useful staging parameters. (Right) Sagittal graphic illustrates supraglottic SCCa. T1 SCCa [] is limited to 1 subsite (L). T2 supraglottic SCCa [] invades more than 1 adjacent subsite or region outside of the supraglottis, such as the vallecula [] (R).

Axial Graphic of Larynx Compartments

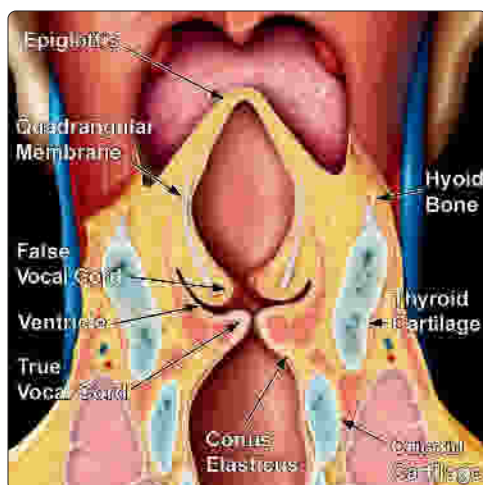


T2 Glottic Tumors

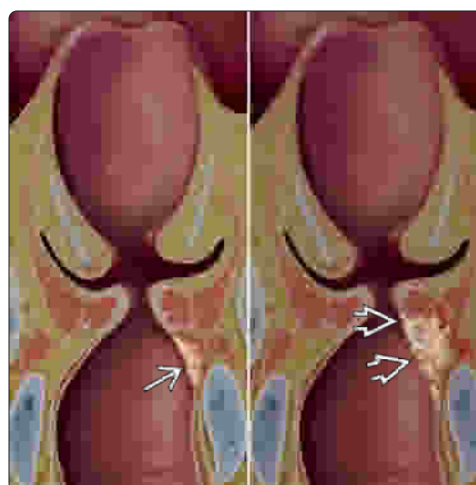


(Left) Axial graphic demonstrates the various compartments and barriers of the larynx. These parameters are important in the staging of tumors of the larynx. The nature barriers can contain the tumor or, with invasion, suggest the specific pathway of metastatic spread. (Right) Graphic demonstrates a T2 glottic SCCa [] extending to supraglottic tissues (top) and a glottic SCCa [] invading the paraglottic fat [] and inner aspect of the thyroid cartilage [] (bottom). Either feature &/or fixation of the vocal cord denotes a T3 glottic SCCa.

Coronal Graphic of Anatomic Landmarks



T1 and T2 Subglottic Larynx Tumors



(Left) Coronal graphic of the larynx at the midcord level demonstrates the anatomic compartments and specific barriers, which would be important in documentation of the primary tumor. (Right) Coronal graphics depict early-stage subglottic tumors. A small T1 SCCa [] is limited only to the subglottis, from the lower aspect of cord and above the inferior cricoid (L). A T2 SCCa [] is shown, extending to the vocal cord (R).

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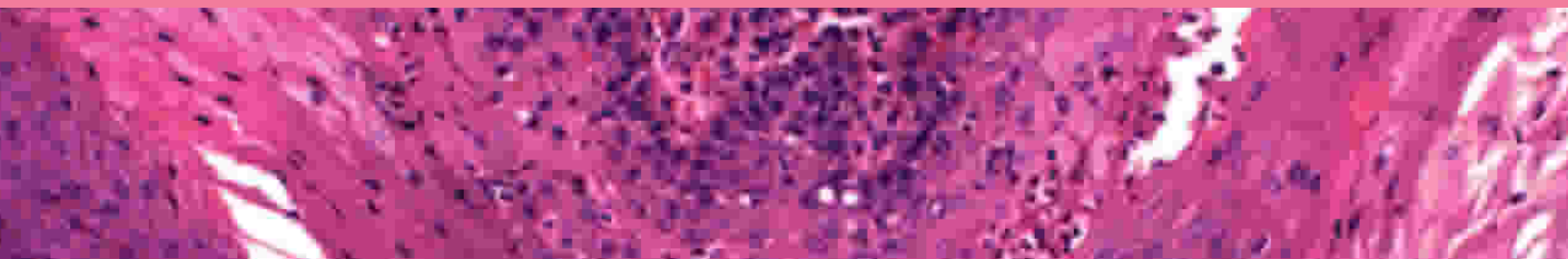
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MACROSCOPIC ANATOMY

Gross Appearance

- Pink, red, or brown in color
- Moist, smooth surface; lack appendages seen in skin

MICROSCOPIC ANATOMY

Epithelium

- Stratified squamous type
- Orthokeratinized in areas exposed to high friction
- Nonkeratinized in most other areas of oral cavity
- Parakeratinized as mucosa transitions to skin on lip
- Rete ridges are present
- Pigmentation: Endogenous or exogenous
- Nonkeratinocytes: Melanocytes, Langerhans cells, Merkel cells, and lymphocytes

Lamina Propria

- Composed of dense connective tissue

- Sebaceous glands (Fordyce granules) are commonly found in lip and buccal mucosa; inflammatory cells variably present

Submucosa

- Dense when overlying bone/periosteum
- Loose when overlying muscle
- Contains blood vessels, nerves
- Minor salivary glands and ducts are present

VARIATIONS

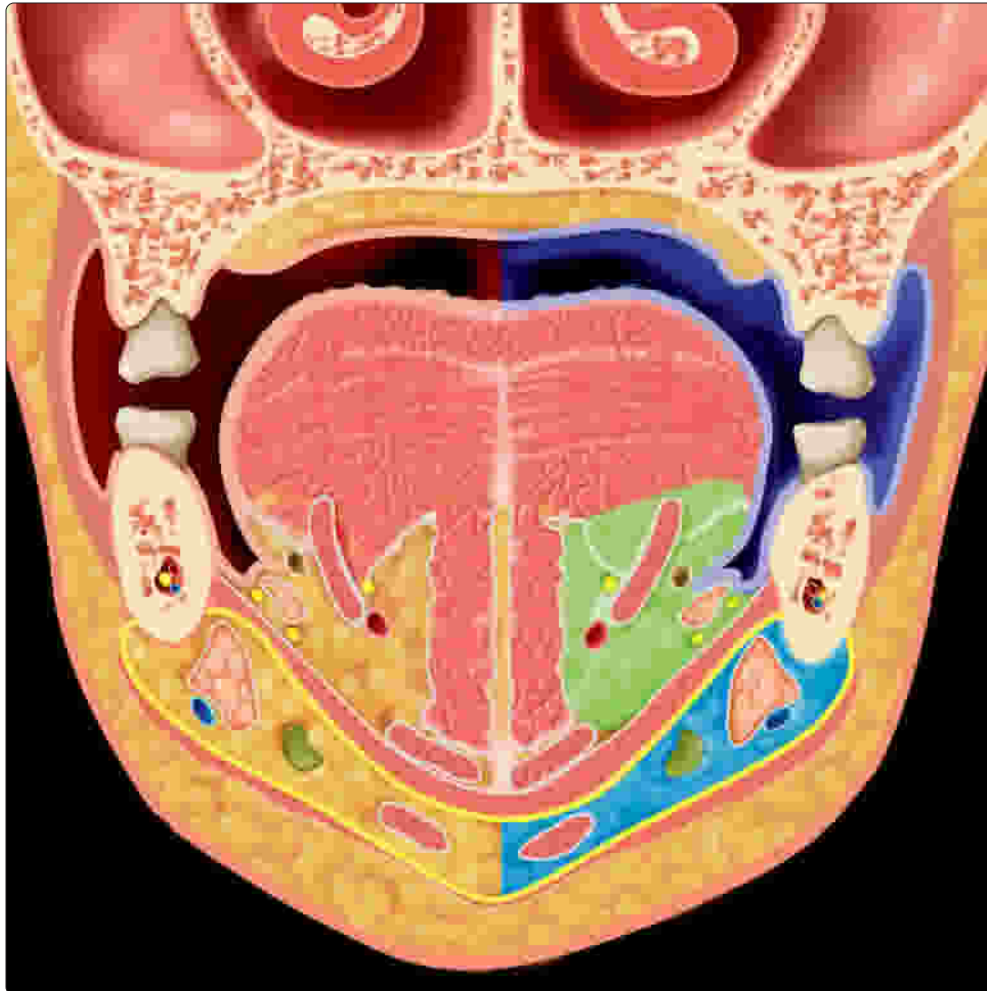
Age-Related

- Epithelium becomes thin and more fragile with aging
- Fordyce granules increase

SELECTED REFERENCES

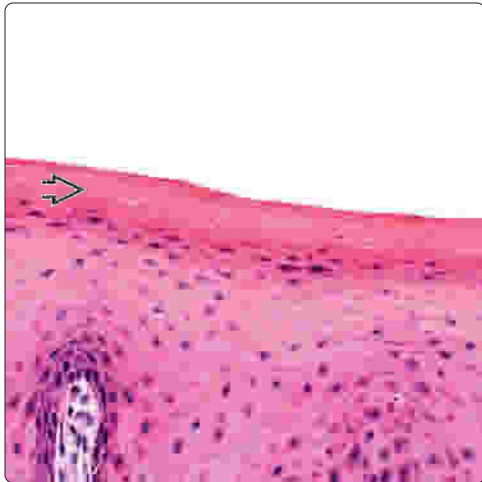
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Graphic of Oral Cavity



The oral cavity is lined with oral mucosae (designated in purple). This protective lining transitions from skin to mucosae at the lips and is continuous with the mucosae of the digestive system. Their protective functions are essential, and the mucosae are also a first-line defense against microorganisms and infection. Oral mucosae are involved in secretion as well as sensations, such as touch, temperature, and taste on the tongue.

Keratinizing Squamous Epithelium

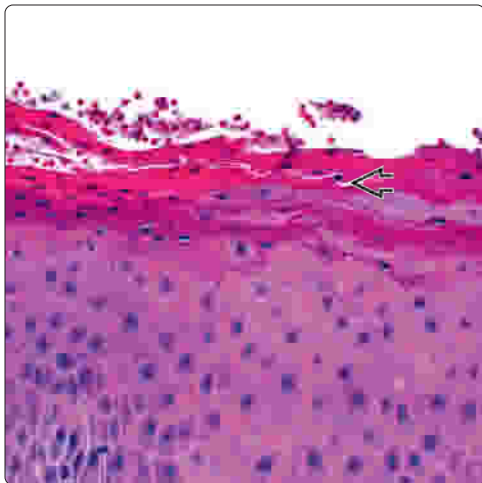


Tongue Papilla With Bacterial Colonies

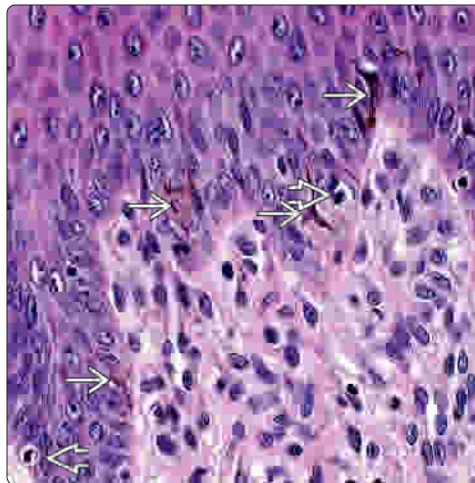


(Left) The keratinization of oral epithelium varies with location and the relative amount of friction to which the tissue is exposed during normal eating or other habits. This image shows epithelium from the palate, surfaced by orthokeratin, flat eosinophilic cells with no nuclei [1]. (Right) This image shows an example of hyperorthokeratotic epithelium seen on the tongue. This appearance is the result of exposure to strong mechanical forces. Note the adherent bacterial colonies [2].

Parakeratinization

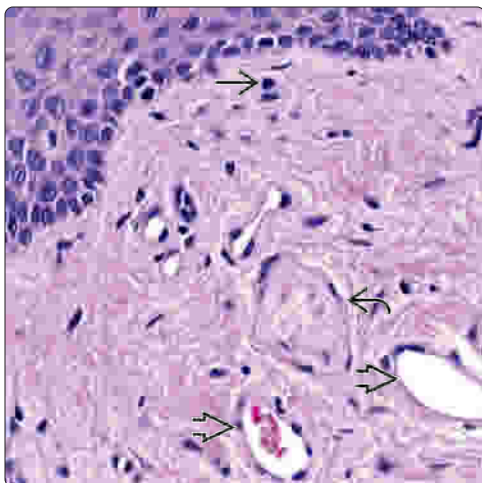


Melanin Pigmentation



(Left) Areas with increased friction or areas like the epithelium near the lips may show areas of parakeratinization, characterized by flat eosinophilic cells with retained pyknotic nuclei [1]. (Right) The color of mucosae varies among individuals, much like the color of skin. This image shows deposition of melanin [2] along the basal layer of epithelium. The number of melanocytes [3] found in the epithelium is generally consistent from one person to the next, despite color variation.

Lamina Propria of Oral Mucosa



Deep Submucosa of Oral Cavity



(Left) This image shows a low-power view of the lamina propria and submucosa. Lymphocytes [1] are a normal finding in the lamina propria. Small blood vessels [2] and nerve twigs [3] are found slightly deeper. (Right) This image shows blood vessels [4], a relatively large salivary gland duct [5] and a minor salivary gland [6] within the submucosa. Deep to these structures, adipose tissue [7] and muscle [8] are seen.

MACROSCOPIC ANATOMY

Separated Into Thirds and Dorsal/Ventral Surfaces

- Anterior 2/3 (mobile tongue) and posterior 1/3 (fixed tongue) separated by sulcus terminalis
- Mobile tongue has dorsal and ventral surfaces
 - Dorsal surface covered by various types of papillae
 - Ventral surface is smooth, lacking papillae
- Majority of tongue parenchyma consists of striated muscle

MICROSCOPIC ANATOMY

Epithelium

- Modified stratified squamous mucosa
 - Ventral surface lined by thin, nonkeratinizing, stratified squamous epithelium with blunt rete pegs
- **Filiform papillae:** Most numerous; line majority of dorsal tongue
 - 2-3 mm long, conical shaped, and curved slightly posteriorly
 - Arranged in vague rows parallel to sulcus terminalis
 - Heavily keratinized and often have oral flora bacterial colonization
- **Fungiform papillae:** Less common, scattered throughout tongue
 - 0.5-1 mm wide, dome-shaped, rise higher than filiform papillae
 - Thin, nonkeratinized epithelium with underlying vascular stroma (appear red-pink in situ)
 - May contain rare taste buds
- **Foliate papillae:** Only found in lateral tongue posteriorly
 - Parallel ridges lined by nonkeratinized stratified squamous mucosa, rudimentary in humans
- **Circumvallate papillae:** Arranged in V-shaped (6-14 papillae) orientation anterior to sulcus terminalis
 - 2-3 mm wide, dome-shaped, surrounded by small circular furrow where most taste buds reside
 - Serous (von Ebner) glands secrete into furrow base and serve to rinse out furrow contents

- Peripheral to furrow and papilla is circular mucosal elevation (the vallum) that may have taste buds
- **Taste buds:** Sensory taste receptors that communicate with surface via gustatory pore
 - Oval-shaped, comprised of 3 cell types: Gustatory (taste), supporting (sustentacular), and basal (regenerative)
 - Gustatory (taste) cells are crescent-shaped, simple epithelial cells with pale cytoplasm innervated by nonmyelinated nerves
 - Nonmyelinated nerve fibers communicate with myelinated fibers in papillae connective tissue core, forming subgemmal nerve plexus
 - Besides papillae, taste buds can be seen in glossopalatine arch, soft palate, lingual epiglottis, and posterior pharynx

Parenchyma

- Majority of tongue parenchyma comprised of interlacing striated muscle (intrinsic) bundles arranged horizontally, vertically, and longitudinally
 - Orientation ensures high mobility to enhance mastication, phonation, swallowing, etc.
 - Varying amounts of mature adipose tissue located between skeletal muscle bundles
 - Extrinsic muscles originate outside of tongue proper
 - Richly vascular and nerve supply
- Small amount of loose connective tissue located between epithelial surface and underlying muscle
- Seros minor salivary glands (von Ebner glands) present only underlying circumvallate papillae
- Mucous minor salivary gland lobules present in muscle in posterior portion of mobile tongue

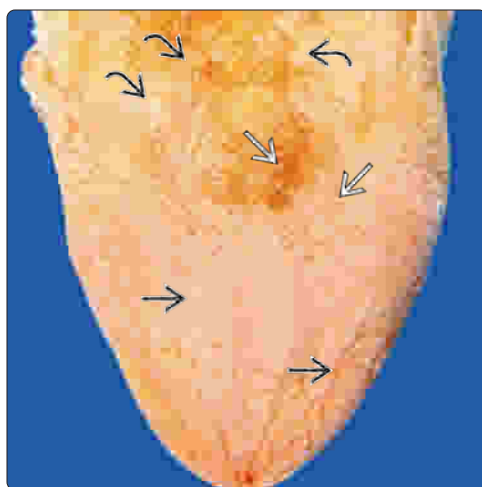
PITFALLS/ARTIFACTS

Pitfalls

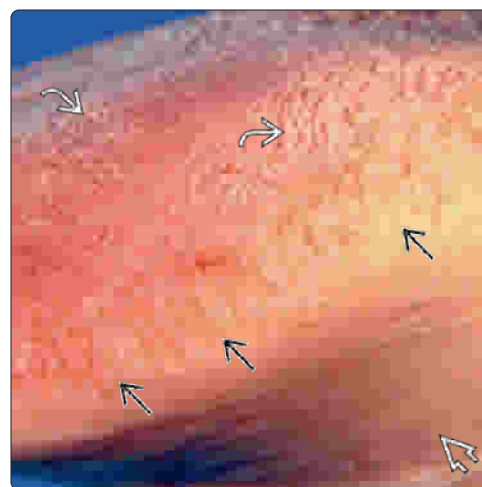
- Salivary gland tissue may be intimately associated with nerves, mimicking perineural invasion
- Neural tissue in connective tissue cores of papillae may be confused with neuromas
- Ectopic tonsil can mimic neoplasms or inflammatory lesions

Anatomy of Dorsal Tongue

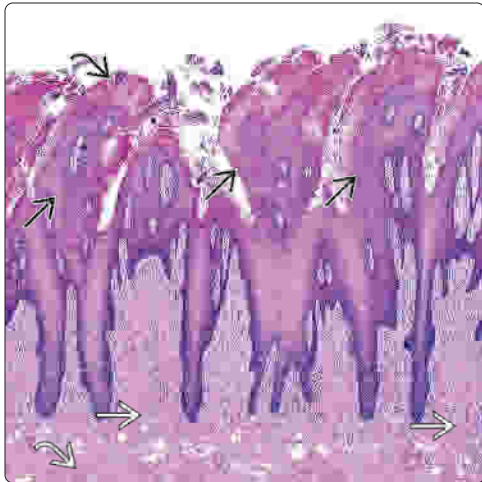
(Left) The posterior border of the mobile tongue consists of a V-shaped row of circumvallate papillae. The dorsal tongue has numerous filiform papillae and scattered fungiform papillae. (Right) The linear foliate papillae are found on the posterior lateral tongue. Note the numerous filiform papillae on the dorsal tongue. The ventral tongue is smooth, lacking papillae.



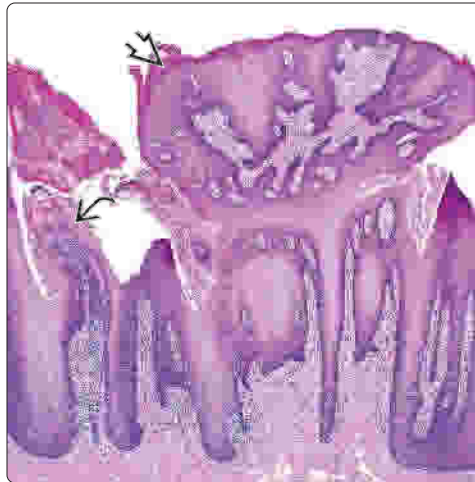
Various Papillae of Tongue



Histology of Filiform Papillae

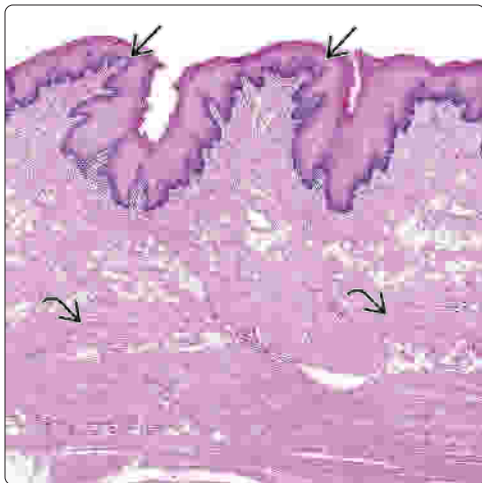


Histology of Fungiform Papilla

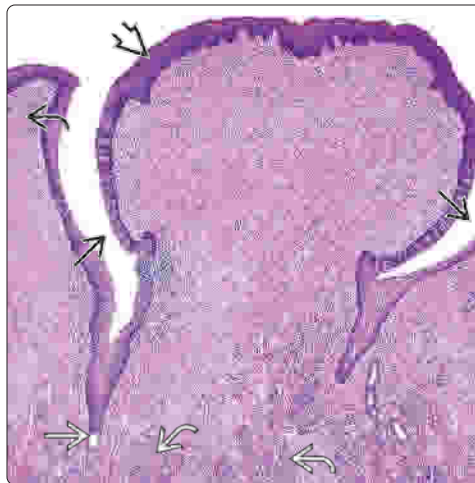


(Left) The dorsal tongue is carpeted with conical-shaped, 2-3 mm long, filiform papillae. Unique, the filiform papillae are heavily keratinized, especially on the tips. There is only a small amount of loose connective tissue between the mucosa and the underlying striated tongue muscle. (Right) Fungiform papillae, 2nd most numerous, are irregularly distributed throughout the tongue between the filiform papillae. These are 0.5-1 mm wide, dome-shaped, and slightly taller than the filiform papillae.

Histology of Foliate Papilla

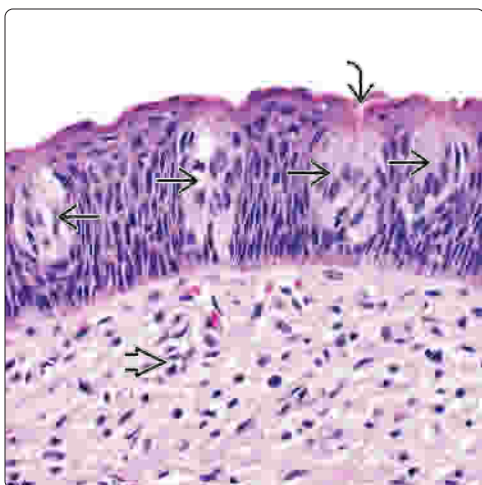


Histology of Circumvallate Papilla

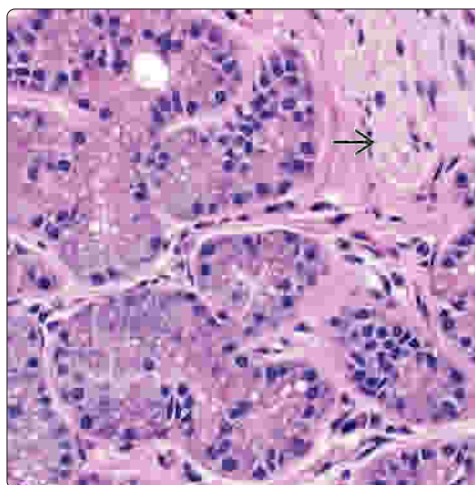


(Left) Unlike in some mammals, foliate papillae are rudimentary in humans. Note the small amount of loose connective tissue separating the mucosa from the striated muscle. (Right) The dome-shaped circumvallate papillae are surrounded by a circumferential furrow and a circular mucosal ridge (vallum) lateral to that. The von Ebner serous glands empty into the base of the furrow and are thought to flush out its contents.

Histology of Taste Buds



Histology of von Ebner Glands



(Left) Taste buds are oval, clear-staining structures comprised of crescent-shaped taste, supporting, and basal cells. A taste pore transmits tastes via receptors on microvilli to the underlying neurites. (Right) The von Ebner glands are serous glands located only below the circumvallate papillae. Their ducts drain into the furrows to flush out its contents. Both serous and mucous glands in the tongue are intimately associated with nerves.

Ectopic (Lingual) Thyroid

KEY FACTS

TERMINOLOGY

- Developmental anomaly due to failure of thyroid gland to descend to normal prelaryngeal site during embryologic development

ETIOLOGY/PATHOGENESIS

- During embryogenesis, thyroid tissue descends from foramen cecum located at midline dorsal tongue along thyroglossal tract
- > 90% occur in tongue
- Cause of thyroid descent failure is unknown

CLINICAL ISSUES

- Uncommon (incidence of 1 in 100,000)
- Seen in all ages (mean: 44 years)
- Female > male (range 4:1 up to 7:1)
- Dysphagia most common symptom
- Other symptoms include foreign body or globus sensation, dysphonia, hemorrhage, and stridor

- In > 75% of patients with lingual thyroid, it is **only** functioning thyroid
- Posterior 2/3 of midline dorsal tongue
- Preoperative work-up includes Tc-99m pertechnetate scanning or radioiodine studies
- Complete or partial surgical excision for symptomatic patients

MICROSCOPIC

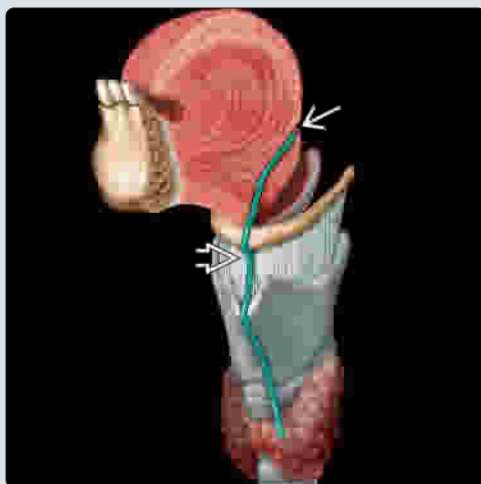
- Normal-appearing thyroid tissue
- Unencapsulated
- May be nodular and hypercellular (goiter clinically)

TOP DIFFERENTIAL DIAGNOSES

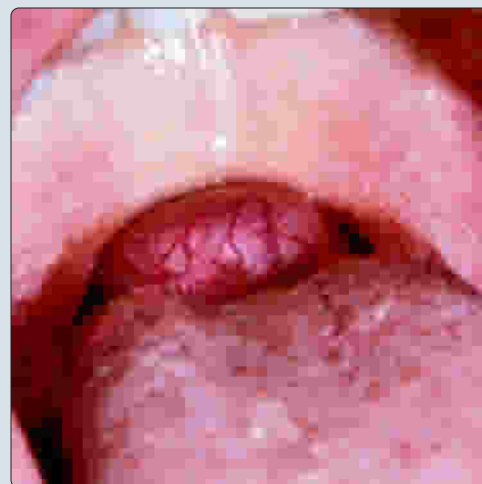
- Microscopic findings are pathognomonic
- Exclude papillary thyroid carcinoma (rare)

Embryological Descent of Thyroid Gland

(Left) The path of descent of the thyroid gland from the foramen cecum to the normal location in the neck can be arrested. Lingual thyroid involves the tongue base. (Right) Clinical photograph shows a lingual thyroid that presents as a smooth, sessile, hyperemic mass on the dorsal tongue just posterior to the circumvallate papillae.

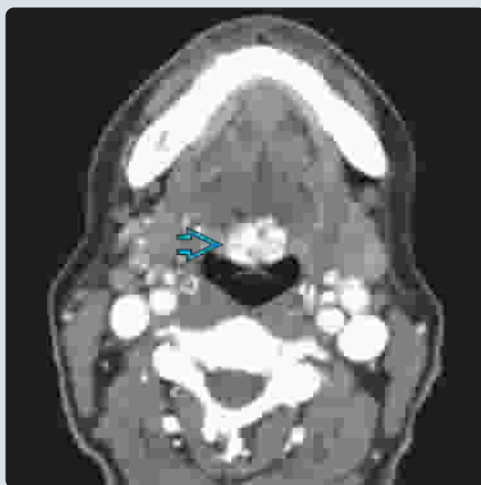


Lingual Thyroid

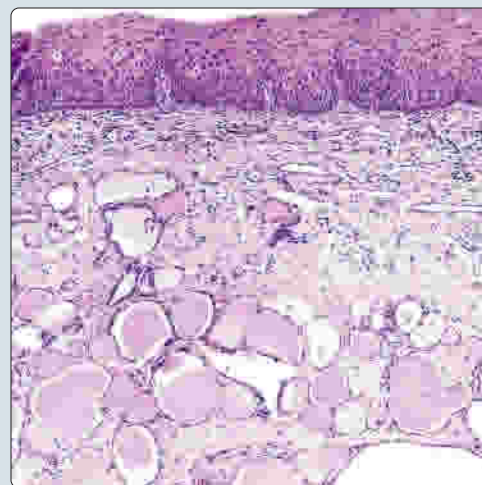


CT Imaging of Lingual Thyroid

(Left) Axial CT of a lingual thyroid with IV contrast shows a large, well-defined mass with distinct margins localized at the tongue base. (Right) H&E shows ectopic lingual thyroid. Normal stratified squamous epithelium overlies benign, unencapsulated thyroid follicles, which interdigitate between the surrounding connective tissue and muscle.



Ectopic Thyroid Tissue in Tongue



TERMINOLOGY

Definitions

- Developmental anomaly due to failure of thyroid gland to descend to normal prelaryngeal site during embryologic development

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- During embryogenesis, thyroid tissue descends from foramen cecum located at midline dorsal tongue along thyroglossal tract
- Ectopic thyroid tissue can be found anywhere along course of thyroglossal tract
 - > 90% occur in tongue
 - Mostly occur between foramen cecum and epiglottis
 - Rarely seen anterior to foramen cecum

Pathogenesis

- Cause of thyroid descent failure is unknown

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon, reported incidence of 1 in 100,000
- Age
 - Seen in all ages (mean: 44 years)
- Sex
 - Female > male (range 4:1 up to 7:1)

Site

- Posterior 2/3 of midline dorsal tongue

Presentation

- Dysphagia most common symptom
- Dyspnea may result if thyroid grows
- Other symptoms include foreign body or globus sensation, dysphonia, hemorrhage, and stridor
- 1/3 of patients with lingual thyroid are hypothyroid
 - In > 75% of patients with lingual thyroid, it is **only** functioning thyroid

Treatment

- Options, risks, complications
 - Preoperative work-up includes Tc-99m pertechnetate scanning or radioiodine studies
 - Will identify normal thyroid gland, if present
 - Will identify any other possible ectopic thyroid
 - Incisional biopsies may cause necrosis or sloughing of lingual thyroid
 - Fine-needle aspiration can confirm diagnosis of ectopic thyroid
- Surgical approaches
 - Complete or partial surgical excision for symptomatic patients
 - Transoral robotic surgery (TORS) vs. extraoral approach
 - In absence of normal located thyroid gland &/or absence of other functioning thyroid gland, surgical resection results in hypothyroidism, necessitating thyroid hormone replacement therapy

- Radiation
 - ¹³¹Iodine will shrink mass
 - Useful in nonsurgical candidates
 - Therapy not selective and can affect normal thyroid tissue in normal location, if present
- Suppression therapy
 - Thyroxin will reduce size, thereby relieving symptoms

Prognosis

- Excellent
- Rare reports of malignant transformation (< 1%)

MICROSCOPIC

Histologic Features

- Normal-appearing thyroid tissue
 - Variably sized follicles lined by cuboidal epithelium
 - Lumen containing proteinaceous colloid material
- Unencapsulated
- Thyroid tissue in submucosa, possibly extending into tongue skeletal muscle
- May be nodular and hypercellular (goiter clinically)

ANCILLARY TESTS

Immunohistochemistry

- Generally unnecessary in diagnosis
- **Positive** staining with thyroglobulin, TTF-1 (nuclear), pax-8 (nuclear), CD56, cytokeratins, and EMA

DIFFERENTIAL DIAGNOSIS

Clinical DDX

- Vascular anomaly
 - Lymphangioma; hemangioma
- Abscess
- Hyperplastic lingual tonsil

Pathologic DDX

- Microscopic findings are pathognomonic
- Exclude papillary thyroid carcinoma (rare)

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Nodular hyperemic mass at base of tongue

Pathologic Interpretation Pearls

- Normal-appearing thyroid follicles, usually unencapsulated

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White Sponge Nevus

KEY FACTS

TERMINOLOGY

- Rare autosomal dominant genodermatosis exhibiting marked leukokeratosis

ETIOLOGY/PATHOGENESIS

- Autosomal dominant disease with incomplete penetrance and variable expressivity
- Mutations in keratin 4 and 13, which are specific type I and type II keratin pairs that form spinous layer

CLINICAL ISSUES

- Disease progression usually stops after puberty
- No reports of malignant transformation
- Exact prevalence unknown, but estimated to affect < 1 in 200,000 individuals worldwide; autosomal dominant with variable expressivity
- Buccal mucosa most common intraoral site
- Other intraoral sites include lip, tongue, palate, and floor of mouth

- Extraoral mucosal sites have been reported but are not common

MICROSCOPIC

- Marked parakeratosis and acanthosis
- Vacuolation or clearing of spinous cell layer

ANCILLARY TESTS

- Pathognomonic perinuclear condensation of keratin tonofilaments on PAP stain
- Perinuclear eosinophilic condensation seen on electron microscopy represents masses of keratin tonofilaments

TOP DIFFERENTIAL DIAGNOSES

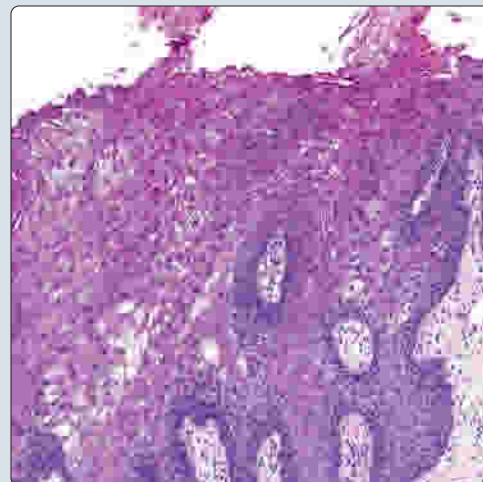
- Hereditary benign intraepithelial dyskeratosis
 - Dyskeratotic cells in spinous layer appears surrounded by adjacent epithelial cell (cell-within-cell)
- Leukoedema
- Oral hairy leukoplakia
 - Balloon cells in upper spinous layer **positive** for EBV

White Sponge Nevus

(Left) Clinical photo shows a typical appearance of white sponge nevus of the buccal mucosa presenting as thick, white, folded plaques. (Right) Medium-power photomicrograph of a WSN shows prominent parakeratosis, acanthosis, and spongiosis. Inflammation is not usually present.

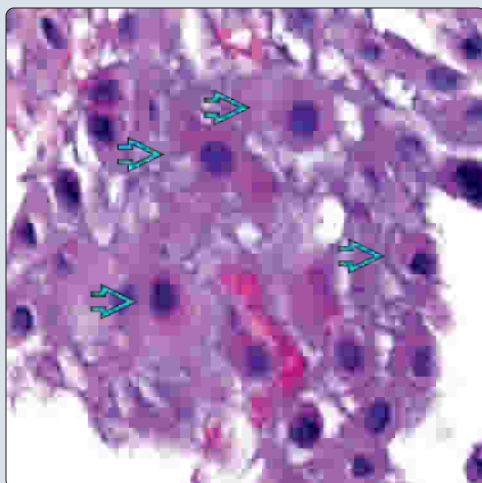


White Sponge Nevus Histology

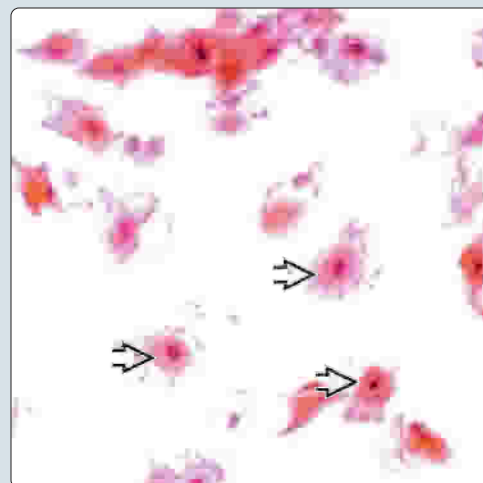


White Sponge Nevus

(Left) High-power photomicrograph of WSN from the spinous layer depicts the characteristic perinuclear eosinophilic condensation of keratin tonofilaments. (Right) Characteristic perinuclear eosinophilic condensation of the keratin tonofilaments are highlighted in a PAP-stained exfoliative cytology. (Courtesy B.W. Neville, DDS.)



White Sponge Nevus, Cytology



KEY FACTS

TERMINOLOGY

- Synonym: Multifocal epithelial hyperplasia
- Benign, virus-induced epithelial proliferation of oral mucosa associated with HPV types 13 and 32

ETIOLOGY/PATHOGENESIS

- Other HPV genotypes, including 1, 6, 11, 16, 18, and 55, have been detected
- > 1 genotype has been detected in same patient

CLINICAL ISSUES

- Majority of reported cases are in children (2-13 years)
- Female predilection with F:M ratio reported as high as 5:1
- Multiple 0.3-1.0 cm mucosal colored soft papules
- Papules can coalesce to form clusters with cobblestone appearance
- Occur mostly on labial and buccal mucosa and tongue
- Lesions often regress spontaneously
- No malignant potential has been reported

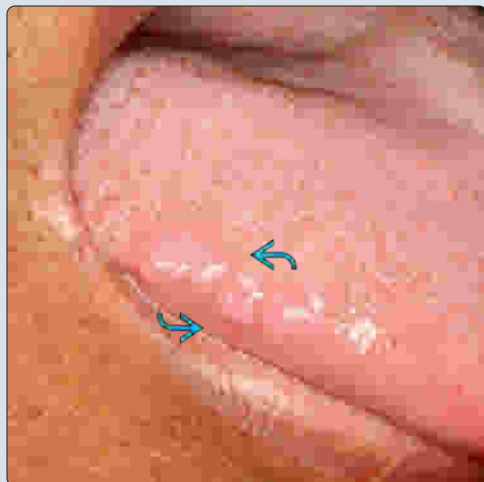
MICROSCOPIC

- Prominent acanthosis
- Elongated broad rete ridges
 - Since focal epithelial hyperplasia (FEH) extends upward, elongated rete are at same depth as adjacent normal rete ridges
- **Mitosoid cells** should not be interpreted as atypia
- Dyskeratosis &/or atypia should not be seen
- HPV 13 or 32 detected in 75-100% of reported cases by DNA in situ hybridization

TOP DIFFERENTIAL DIAGNOSES

- **Microscopic Ddx**
 - Papilloma and condyloma acuminatum
 - Associated with HPV 6 &/or 11
 - Oral verruca vulgaris
 - Associated with HPV types 2, 4, 6, 40, and 57
 - Mucosal neuromas of MEN2
 - Verruciform xanthoma

Multiple Mucosal Papules of Focal Epithelial Hyperplasia

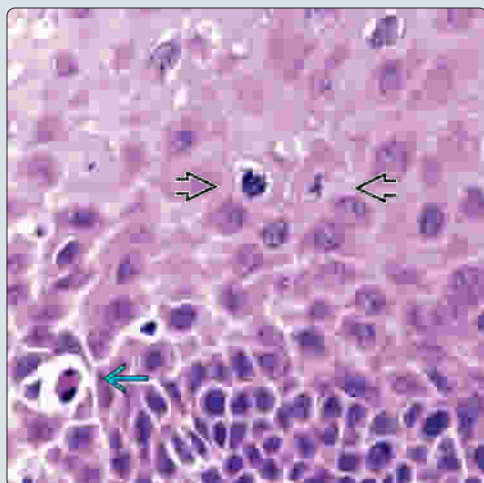


Focal Epithelial Hyperplasia With Acanthosis

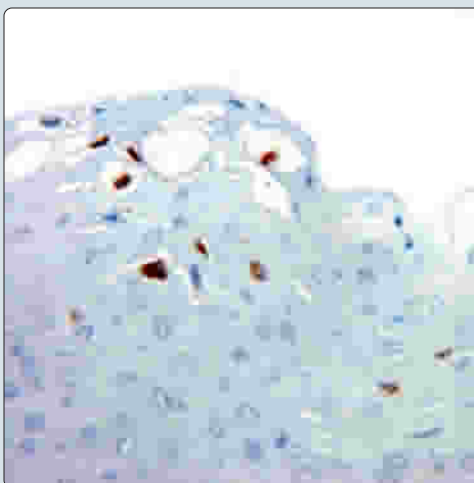


(Left) Focal epithelial hyperplasia presenting as multiple mucosal colored papules and nodules of the lateral tongue [A]. The patient also had lesions on the contralateral side. The lesions usually coalesce, imparting a cobblestone appearance and can appear papillary. (Right) Focal epithelial hyperplasia with prominent acanthosis, elongated rete ridges, and a slightly papillary surface is shown. The papillary features are not always noted. The rete are broad and can fuse, forming horizontal anastomoses.

Mitosoid Cells in Heck Disease



Nuclear Reaction With HPV ISH



(Left) Mitosoid cells [B] that represent an altered nucleus in an otherwise normal stratified squamous epithelium are seen. This can be misinterpreted as an atypical mitotic figure. Dyskeratosis [C] and binucleation can occasionally be observed. (Right) DNA in situ hybridization for HPV13 demonstrates numerous HPV-positive nuclei in the prickly layer of the epithelium.

Hairy Leukoplakia

KEY FACTS

TERMINOLOGY

- EBV-associated epithelial hyperplasia, usually on lateral tongue in immunocompromised patients

ETIOLOGY/PATHOGENESIS

- Oral hairy leukoplakia (OHL) associated with HIV infection &/or immunosuppression
- EBV (HHV-4) linked to OHL; usually latent infections
- Langerhans cells are decreased or absent in OHL

CLINICAL ISSUES

- Although not AIDS-defining disease, it is marker of HIV disease progression
- Lateral border of tongue most commonly affected
- Cases have been reported in both solid organ and bone marrow transplant patients
 - More common in allogeneic transplant patients
- No treatment is needed
- Some cases of OHL spontaneously resolve

MICROSCOPIC

- Marked acanthosis and parakeratosis
- Balloon cells in spinous layer
- Very little, if any, inflammation
- Coinfection with candidiasis
- No dysplasia should be seen

ANCILLARY TESTS

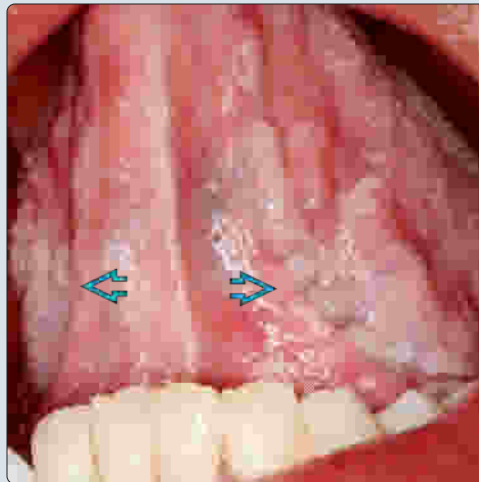
- EBER shows punctate nuclear staining of spinous layer balloon cells

TOP DIFFERENTIAL DIAGNOSES

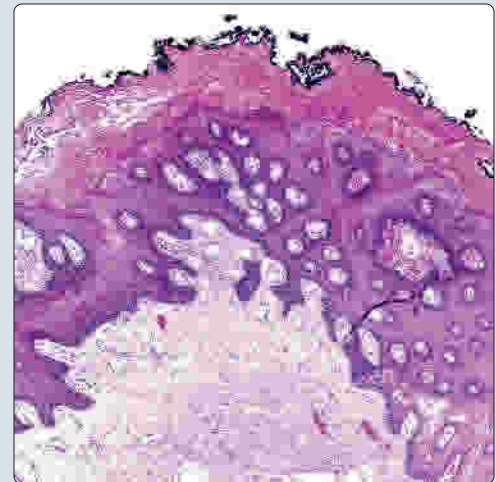
- Frictional keratosis
- Hyperplastic candidiasis
- Leukoplakia
- Lichen planus
- White sponge nevus

Oral Hairy Leukoplakia

(Left) Clinical photograph shows oral hairy leukoplakia in a 44-year-old HIV(+) woman. These asymptomatic lesions are bilateral and extend from the lateral tongue to the ventral tongue. (Right) Oral hairy leukoplakia is characterized by an acanthotic, markedly parakeratotic corrugated epithelium. Note the relative lack of inflammation. Colonies of bacteria are noted on the epithelial surface.

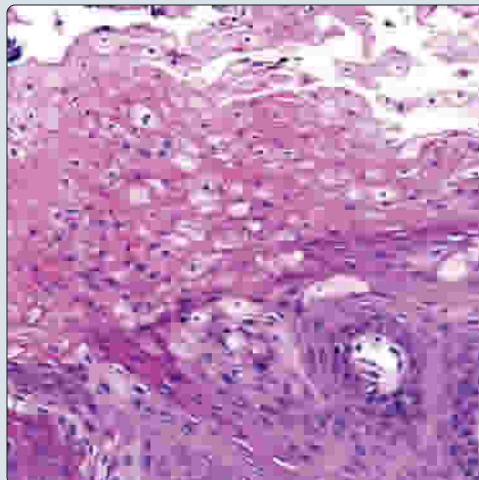


Oral Hairy Leukoplakia, Low-Power Histology

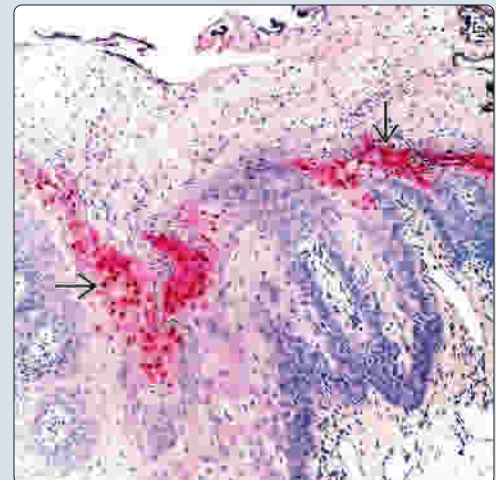


Balloon Cells in Oral Hairy Leukoplakia

(Left) High-power photomicrograph shows balloon cells in the spinous layer of oral hairy leukoplakia. These features are indicative of a viral cytopathic effect. (Right) In situ hybridization for Epstein-Barr virus-encoded RNA (EBER) shows strong punctate nuclear positivity in the area where the balloon cells are identified.



EBER Expression in Oral Hairy Leukoplakia



TERMINOLOGY

Abbreviations

- Oral hairy leukoplakia (OHL)

Definitions

- Epstein-Barr virus (EBV)-associated epithelial hyperplasia, usually on lateral tongue in immunocompromised patients

ETIOLOGY/PATHOGENESIS

Etiology

- OHL associated with HIV infection &/or immunosuppression
- Disease correlates with viral load and CD4 counts in HIV(+) cases

Pathogenesis

- EBV (HHV-4) linked to OHL; usually latent infections

CLINICAL ISSUES

Epidemiology

- Incidence
 - Since advent of highly active antiretroviral therapy (HAART), incidence has decreased to < 10% of HIV population
 - Cases have been reported in both solid organ and bone marrow transplant patients
- Age
 - All ages affected
- Sex
 - Most common in HIV(+) males

Site

- Lateral border of tongue most commonly affected

Presentation

- Epithelial hyperplasia with corrugated appearance
- Lesions are adherent and cannot be scraped off
- Appearance frequently changes, resolving then reappearing
 - Can be extensive, bilateral, and involve dorsal and ventral tongue
- Asymptomatic, unless superimposed *Candida* infection present

Treatment

- No treatment is needed

Prognosis

- Although not AIDS-defining disease, it is marker of HIV disease progression
- Some cases of OHL spontaneously resolve

MICROSCOPIC

Histologic Features

- Marked acanthosis and parakeratosis
- Epithelial hyperplasia with elongation of rete ridges
- Balloon cells in spinous layer
 - Viral cytopathic effect
 - Intracellular ballooning degeneration
 - Nuclear clearing with chromatin margination

- Candidal organisms can be seen in superficial keratin
- Very little, if any, inflammation
- No dysplasia should be seen

ANCILLARY TESTS

Histochemistry

- Fungal stains (PAS or GMS)
 - Highlights candidal organisms

In Situ Hybridization

- EBV-encoded RNA (EBER) shows punctate nuclear staining of spinous layer balloon cells

DIFFERENTIAL DIAGNOSIS

Frictional Keratosis

- Lateral border of tongue is frequent site for inadvertent masticatory trauma
- No balloon cells seen in spinous layer

Hyperplastic Candidiasis

- Oral candidiasis can become hyperplastic and share similar clinical features
- PAS stains show numerous candidal organisms in superficial keratin

Leukoplakia

- Common location for oral leukoplakia
- No EBV etiology
- Various degrees of dysplasia may be seen

Lichen Planus

- Can appear hyperplastic clinically
- Basal cell liquefaction and dense band of lymphocytes and plasma cells adjacent to basal cells
- Dyskeratotic epithelial cells seen at epithelial-connective interface

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- EBV-associated lesion generally present on lateral tongue in HIV(+) males

Pathologic Interpretation Pearls

- Layer of balloon cells in spinous layer positive for EBV by EBER staining
- May see coinfection with candidiasis

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4. Coogan MM et al: Oral lesions in infection with human immunodeficiency virus. *Bull World Health Organ.* 83(9):700-6, 2005
5. Walling DM et al: Effect of Epstein-Barr virus replication on Langerhans cells in pathogenesis of oral hairy leukoplakia. *J Infect Dis.* 189(9):1656-63, 2004

KEY FACTS

TERMINOLOGY

- **Candidiasis:** Most common oral fungal infection with diverse clinical presentation
 - Majority of cases associated with *Candida albicans*
- **Herpes simplex virus type 1 (HSV1):** Caused by human herpesvirus, herpes simplex virus type 1 (a.k.a. HHV-1)
 - Transmission through direct contact of active perioral lesions or infected saliva
 - Recurrent HSV1: Latent virus resides in trigeminal ganglion and becomes reactivated
- **Actinomycosis:** Normal saprophytic gram-positive anaerobic bacteria that can colonize bone and skin
 - > 55% of cases involve cervicofacial region
- **Herpangina:** Common viral infection of young children associated with blisters of soft palate &/or tonsillar pillars
- **Hand, foot, and mouth disease (HFMD):** Common viral illness of infants and children, which causes fever and blister eruptions of mouth &/or skin

MICROSCOPIC

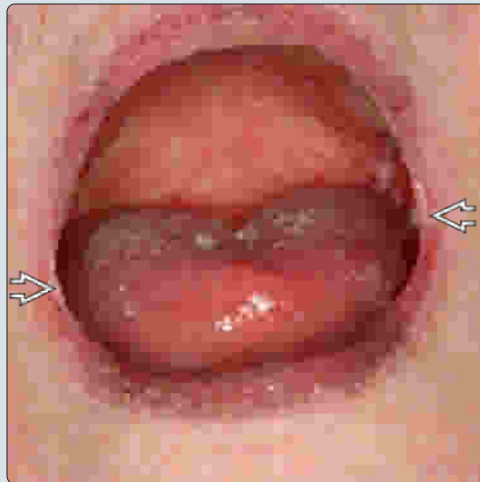
- **Candidiasis:** Organisms can be seen in parakeratin layer highlighted by PAS staining
 - Neutrophilic microabscesses can be seen in keratin layer
 - Pseudoepitheliomatous hyperplasia with markedly elongated rete
- **HSV1:** Infected epithelial cells show acantholysis (Tzanck cells)
 - HSV1 in situ hybridization will demonstrate nuclear staining in virally infected cells
- **Actinomycosis:** Colonies of basophilic, club-shaped bacteria arranged in radiating rosette pattern surrounded by neutrophils
- **Herpangina and HFMD:** Self-limited disease and biopsy rarely done

TOP DIFFERENTIAL DIAGNOSES

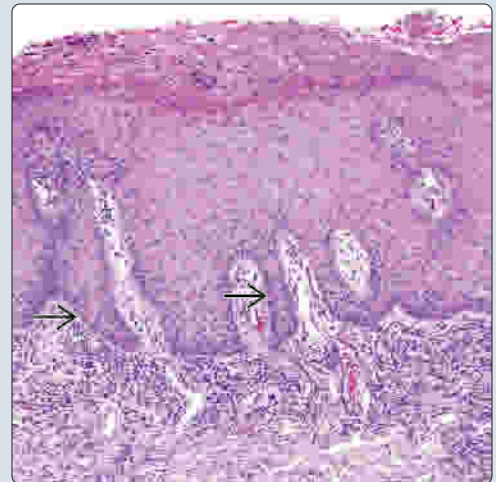
- **Candidiasis:** Geographic tongue; oral dysplasia
- **HSV1:** Erythema multiforme; herpes zoster

(Left) Pseudomembranous candidiasis presenting as multiple white plaques on the tongue and palate. These plaques easily wipe off unlike hyperplastic candidiasis. The patient also has angular cheilitis. (Right) Median rhomboid glossitis shows marked thickening of the parakeratin, inflammatory exocytosis, neutrophilic microabscesses, and elongated epithelial rete with subjacent chronic inflammation. Organisms would be highlighted with PAS.

Oral Candidiasis, Pseudomembranous Type

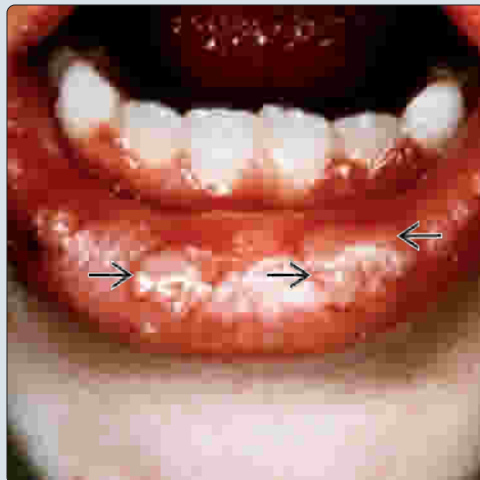


Candidiasis Median Rhomboid Glossitis

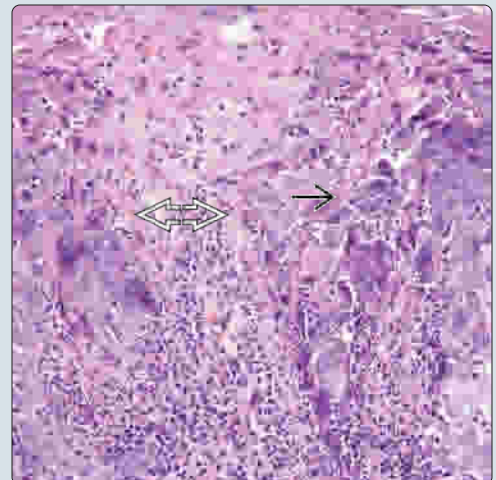


(Left) Primary herpes simplex type 1 (HSV1) (acute herpetic gingivostomatitis) in a young person with numerous ulcers is noted on the lower lip and enlarged, erythematous, and painful gingiva. Depending on the severity of the outbreak, lesions last from 7-14 days. (Right) Biopsy of HSV1 lesion shows a ruptured vesicle with altered epithelial cells. Ballooning degeneration and chromatin condensation around the periphery of the nucleus is noted as well as multinucleation.

Primary Herpes Simplex Type 1



Herpes Simplex Type 1



TERMINOLOGY

Definitions

- **Candidiasis:** Most common oral fungal infection with diverse clinical presentation
 - Majority of cases associated with *Candida albicans*
- **Herpes simplex virus type 1 (HSV1):** DNA virus spread by direct contact or infected saliva
 - Most commonly seen in oral, ocular, or facial region, including pharynx, lips, intraoral area, and skin
- **Actinomycosis:** Normal saprophytic gram-positive anaerobic bacteria that can colonize bone and skin resulting in acute or chronic infection
- **Herpangina:** Common viral infection of young children associated with blisters of soft palate or tonsillar pillars
- **Hand, foot, and mouth disease (HFMD):** Common viral illness of infants and children, which causes fever and blister eruptions of mouth &/or skin

ETIOLOGY/PATHOGENESIS

Candidiasis

- Overgrowth of fungal organisms that may be component of normal oral flora in up to 50% of population
 - Besides *C. albicans*, *Candida tropicalis*, and *Candida krusei* can also cause disease
- Caused by broad spectrum antibiotics, topical or systemic prednisone, anemia, xerostomia, impaired immune system, dentures

Herpes Simplex Virus Type 1

- Acute herpetic gingivostomatitis (primary herpes)
 - Caused by human herpes simplex virus type 1 (a.k.a. HHV-1)
 - Transmission through direct contact of active perioral lesions or infected saliva
 - Incubation period 3-9 days
- Recurrent HSV1
 - Latent virus residing in sensory nerves becomes reactivated
 - Trigeminal ganglion is most common site of latency for head and neck HSV1
 - Reactivation of virus can be triggered by ultraviolet light, physical or mental stress, trauma, dental therapy

Actinomycosis

- Majority of cases caused by *Actinomyces israelii*
- Organisms generally enter soft tissue in area of trauma

Herpangina

- Caused by virus belonging to *Enterovirus* group (poliovirus, coxsackievirus, echovirus)
 - Coxsackie virus A6 and A10 are most common cause, but other Coxsackie viruses can cause disease
- Transmission is direct contact, often oral-fecal route

Hand, Foot, and Mouth Disease

- Caused by virus belonging to *Enterovirus* group
 - Coxsackie A16 virus is most common cause, but other Coxsackie viruses can cause disease
 - Enterovirus 71 is more virulent strain that can affect adults
- Transmission by direct contact from person to person

- Virus found in secretions, including saliva, nose and throat secretions, blister fluid, and stools

CLINICAL ISSUES

Presentation

- **Candidiasis:** Numerous clinical presentations; patient may have more than 1 at once
 - Pseudomembranous candidiasis (thrush) presents with white curd-like plaques that can be removed with scraping
 - Erythematous candidiasis appears as reddened, often atrophic, mucosa with associated burning
 - **Median rhomboid glossitis** presents as central area of erythema on dorsal tongue with atrophic papillae
 - **Denture stomatitis** presents as erythema under full or partial denture
 - **Angular cheilitis** presents as erythematous fissured areas at corners of mouth
 - Hyperplastic candidiasis composed of white plaques that cannot be wiped off
 - Can be difficult to separate from oral leukoplakia secondarily superimposed with *Candida*
 - Mucocutaneous candidiasis
 - Seen in association with immunologic disorders involving endocrine system
- **HSV1**
 - Primary HSV1
 - < 15% of patients exhibit clinical manifestations of initial HSV1 infection
 - Abrupt onset of symptoms, including fever, nausea, chills, lymphadenopathy, and stomatitis
 - Gingiva becomes erythematous, painful, and enlarged
 - Numerous irregular coalescing ulcers throughout oral cavity
 - Generally, lesions are present intra-/periorally, pharynx, facial skin, and skin above waist
 - Halitosis
 - Recurrent HSV1
 - Most common site is vermilion border or surrounding skin of lip (herpes labialis, fever blister)
 - Often experience prodrome of tingling, itching, and pain of affected site anywhere from 6-36 hours
 - Clusters of fluid-filled vesicles develop and rupture within 2 days, then form crust
 - Intraoral recurrences are seen on keratinized mucosa, including hard palate and attached gingiva
- **Actinomycosis**
 - > 55% of actinomycosis involve orocervicofacial region
 - May be rapidly progressing acute infection or chronic
 - Suppurative abscesses may contain yellow flecks (**sulfur granules**), which are colonies of bacteria
 - Direct extension into soft tissue may result in sinus tract
 - Fibrosis of indurated soft tissue
 - Actinomycotic osteomyelitis of jaws has been reported
- **Herpangina**
 - Disease begins with acute onset of fever and sore throat
 - Other symptoms include poor appetite, dysphagia, myalgia, diarrhea, vomiting, and headache
 - Small, 2-4 mm, red macules that form vesicles, numbering 2-6, occur in oropharynx

- Constitutional symptoms resolve in days
- Mouth ulcers resolve usually in 7-10 days
- **HFMD**
 - Disease usually presents with malaise, fever, and poor appetite
 - ~ 48 hours after fever onset, blisters develop in mouth (tongue, gums, and buccal mucosa)
 - Nonpruritic cutaneous rash may develop on palms and soles and sometimes buttocks and genitalia

Laboratory Tests

- **Candidiasis**
 - Culture can definitively identify organism
 - Specificity and sensitivity generally only needed in treatment-resistant cases
- **HSV1**
 - Virologic testing can be done but not as accurate as newer tests
 - Polymerase chain reaction (PCR) is used but more often reserved for spinal fluid
 - Serologic tests may be negative if testing right after initial exposure
 - To prevent false-negatives, testing should be done 12-16 weeks after exposure
 - Enzyme-linked immunosorbent assay highly accurate in typing HSV
- **Actinomycosis**
 - Isolation via culture is difficult because of other bacterial contaminants or prior antibiotic treatment
- **Herpangina**
 - Throat or stool samples can be sent for viral culture
 - PCR has been used to rapidly identify specific *Enterovirus*
- **HFMD**
 - Throat, cutaneous, or stool samples can be sent for laboratory testing to identify specific *Enterovirus*
 - Rarely done since test takes 2-4 weeks, and HFMD is self-limiting

Treatment

- **Candidiasis**
 - Topical &/or systemic antifungal therapy
 - Biopsy often employed to diagnose disorder
- **HSV1**
 - Systemic antivirals for primary HSV1
 - Topical &/or systemic antivirals for recurrent HSV1
- **Actinomycosis**
 - Incision and drainage of abscesses
 - Long-term intravenous antibiotic (penicillin, amoxicillin) for chronic cases or osteomyelitis
- **Herpangina and HFMD**
 - Supportive therapy for constitutional symptoms

MICROSCOPIC

Histologic Features

- **Candidiasis**
 - Organisms can be seen in parakeratin layer highlighted by PAS staining
 - Branching hyphae, 2 µm in diameter with ovoid spores
 - Neutrophilic microabscesses can be seen in keratin layer
 - Inflammatory cell exocytosis

- **HSV1**
 - Infected epithelial cells show acantholysis (Tzanck cells)
 - Ballooning degeneration of nuclei with chromatin condensation along periphery
 - Infected cells can fuse to form multinucleated cells
 - HSV1 in situ hybridization will demonstrate nuclear staining in virally infected cells
- **Actinomycosis**
 - Colonies of basophilic club-shaped bacteria arranged in radiating rosette pattern surrounded by neutrophils
 - Granulation tissue and nonvital bone
- **Herpangina and HFMD**
 - Self-limited disease and biopsy rarely done

DIFFERENTIAL DIAGNOSIS

Candidiasis

- Geographic tongue: Can see neutrophilic microabscesses in epithelium
- Oral dysplasia can be secondarily infected
 - Sometimes difficult to distinguish reactive atypia to fungal organisms and true dysplasia
 - Rebiopsy may be indicated after appropriate treatment
- Radiation mucositis: Bizarre epithelial and stromal cells
- *Candida* can be associated with intense inflammatory infiltrate mimicking lichen planus

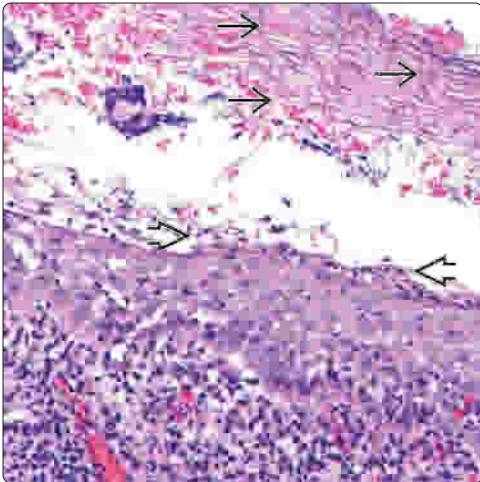
HSV1

- Erythema multiforme (EM)
 - Need clinical correlation
 - Target lesions on skin in EM but not in HSV1
- Necrotizing ulcerative gingivitis
 - Lesions confined to gingiva
- Herpes zoster
 - Microscopically identical to HSV1
 - In situ hybridization will be able to distinguish between herpesvirus subtypes

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Candidiasis Hyphae Forms



Recurrent Herpes Simplex 1

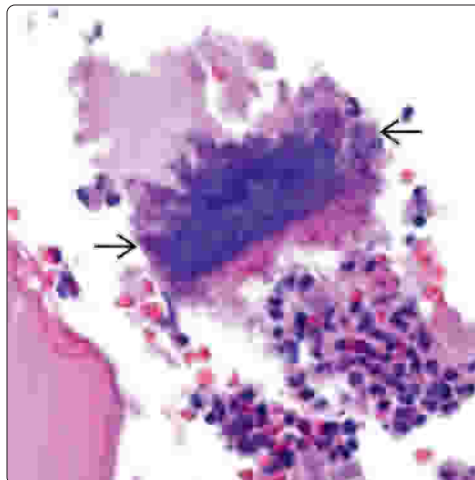


(Left) Hyperplastic candidiasis exhibits marked keratoses with neutrophilic microabscesses in the superficial keratin. The detached keratin contains numerous fungal organisms. (Right) Recurrent HSV1 can occur intraorally. It is generally seen on the keratinized tissue attached to bone, such as the hard palate and attached gingiva. In the immunosuppressed patient, lesions can occur anywhere in the oral cavity and may be chronic.

Actinomycosis

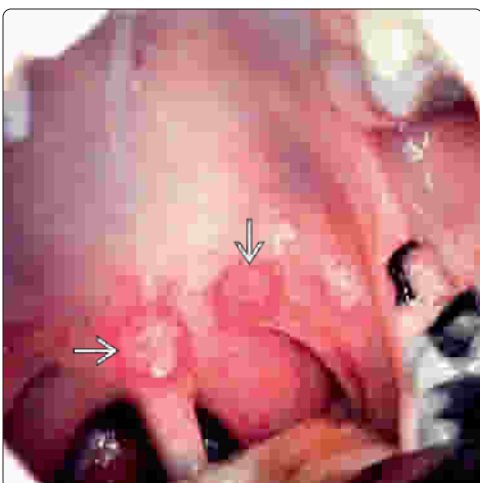


Actinomycosis



(Left) Chronic draining fistula of the submandibular area is shown; culture was positive for actinomycosis. Yellowish flecks, which represent actinomycotic colonies (sulfur granules), may be noted in the suppurative area. (Right) Actinomycosis shows the characteristic club-shaped, filamentous organisms arranged in a radiating rosette pattern. Adjacent nonvital bone and neutrophils are noted. This was associated with osteonecrosis of the mandible.

Herpangina



Hand, Foot, and Mouth Disease



(Left) Herpangina is seen as large, aphthous-like ulcerations of the soft palate, which start as small vesicles that rapidly ulcerate and last 7-10 days. Herpangina differs from hand, foot and mouth disease (HFMD) where ulcers occur throughout the mouth. (Right) HFMD is shown with characteristic vesicles on the palm. The lesions start as erythematous macules and then develop central vesicles, which heal without crusting. The ulcers are preceded by flu-like symptoms, including fever, sore throat, and myalgia.

KEY FACTS

ETIOLOGY/PATHOGENESIS

- Allergens thought to play role in triggering recurrent aphthous stomatitis (RAS)
 - Cinnamon, cereal products, chocolate, nuts, and certain fruits and vegetables have been cited

CLINICAL ISSUES

- Widely reported incidence (average: 35%)
- Lesions arise almost exclusively on nonkeratinized mucosa
- Minor RAS: Most common type; affects 80% of RAS patients
- Major RAS: > 1 cm ulcers that can last for several weeks
- Herpetiform RAS present as clusters of small ulcers ranging from 1-3 mm
- Typically treated with topical and systemic corticosteroids

MICROSCOPIC

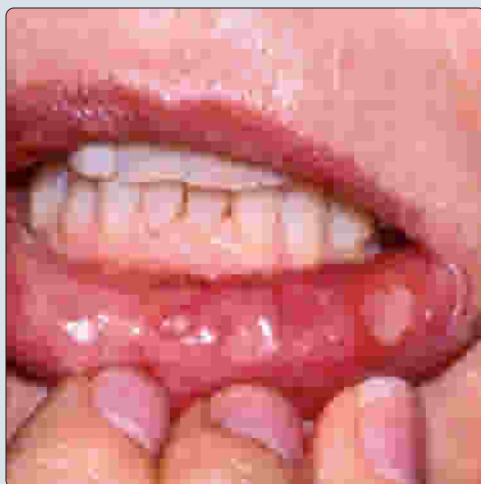
- No unique microscopic features
- Early lesion: Ulceration with fibrinopurulent membrane

TOP DIFFERENTIAL DIAGNOSES

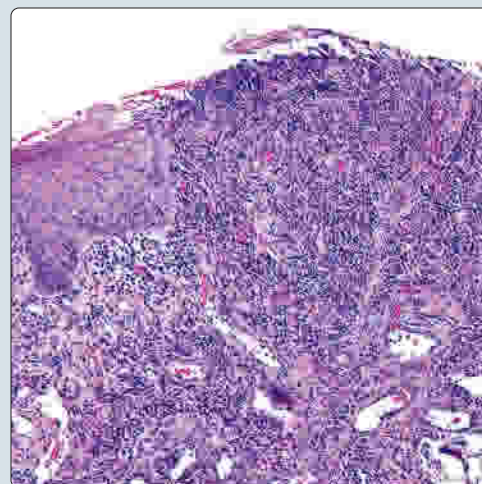
- Behçet disease (BD)
 - Microscopic features similar to RAS
- Reiter disease (reactive arthritis)
 - Oral lesions seen in < 20% of cases
 - Biopsy of circinate area of tongue similar in appearance to geographic tongue or psoriasis
- Crohn disease (regional ileitis; regional enteritis)
 - May see noncaseating granulomatous inflammation
- Traumatic ulcerative granuloma
 - Histologically, inflammation extends much deeper into striated muscle, with sheets of histiocytes and lymphocytes with scattered eosinophils
- Recurrent herpes simplex virus type 1 (HSV-1)
 - Most HSV-1 ulcers: Lip vermillion; intraoral lesions: Keratinized mucosa (hard palate, attached gingiva)
 - Acantholytic epithelial cells seen in ulcer (Tzanck cells)
 - Older HSV-1 lesions: Indistinguishable from RAS

Minor Recurrent Aphthous Ulcer

(Left) Clinical photograph shows minor recurrent aphthous ulcer. The < 1 cm ulcer has a red halo surrounding the ulcer bed that clinically appears as a yellow fibrinous membrane. The ulcer is arising on nonkeratinizing mucosa. **(Right)** Hematoxylin and eosin shows an aphthous ulcer. Histology is that of a nonspecific ulcer with a fibrinopurulent membrane. A mixed inflammatory cell infiltrate is seen beneath the ulcer bed.

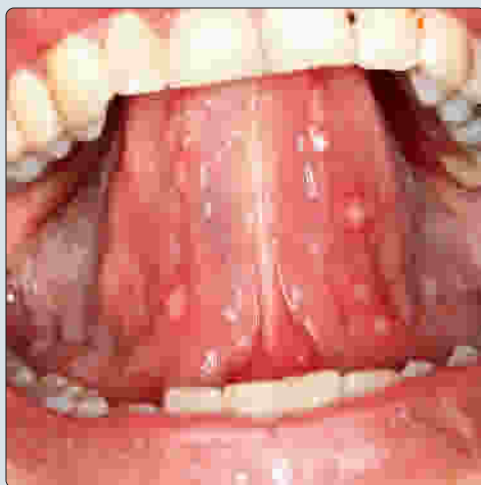


Aphthous Ulcer Histology



Aphthous Ulcer, Herpetiform Variant

(Left) Clinical photograph shows herpetiform aphthous ulcers. Despite the name, these ulcers do not have an infectious etiology. Clusters of numerous 1-3 mm ulcers are seen throughout the ventral tongue. Patients may experience as many as 100 ulcers at a time. **(Right)** Clinical photograph shows a major aphthous ulcer presenting on the tonsillar pillar. These ulcers are quite painful and may produce reactive lymphadenopathy. Because of the ulcer size, resolution may take several weeks.



Aphthous Ulcer, Major Form



TERMINOLOGY

Abbreviations

- Recurrent aphthous stomatitis (RAS)

Synonyms

- Recurrent aphthous ulcerations, canker sores

Definitions

- Noninfectious, common T cell-mediated nonkeratinized mucosal ulceration

ETIOLOGY/PATHOGENESIS

Multifactorial

- Allergens thought to play role in triggering RAS
 - Cinnamon, cereal products, chocolate, nuts, and certain fruits and vegetables have been cited
- Mechanical trauma, such as orthodontia
- Stress and anxiety
- Nutritional deficiencies, including vitamin B12
- RAS demonstrates familial tendency
 - If both parents have RAS, 90% likelihood that offspring will develop RAS
- No known association with infectious agents, such as herpes, *Streptococcus*, and *Helicobacter pylori*

Immunology

- Precise initiating event unknown
- Peripheral blood in patients with RAS show decreased CD4:CD8 cells ratio and increased tumor necrosis factor- α
- Localized mucosal destruction due to local T cell-mediated response
 - TNF- α generated by T cells, macrophages, and mast cells result in tissue destruction

CLINICAL ISSUES

Epidemiology

- Incidence
 - Widely reported range (average: 35%)
- Age
 - RAS starts in childhood and adolescence and persists into adulthood
- Sex
 - Equal gender distribution

Presentation

- Minor RAS
 - Most common type; affects 80% of RAS patients
 - Lesions arise almost exclusively on nonkeratinized mucosa
 - Buccal mucosa and lip are most common locations
 - Often RAS present as multiple ulcers
 - May be preceded by prodrome of burning or stinging
 - Painful ulcer ≤ 1 cm, covered by yellow fibrinopurulent membrane surrounded by erythematous border
 - Heals without scarring in 7-14 days
 - Recurrences can range from every few weeks to every few years
 - Some patients who experienced very few aphthous ulcers in past may develop more frequent outbreaks for no known cause

- Major RAS
 - > 1 cm ulcers that can last for several weeks
 - Soft palate and tonsillar pillar are most common locations
 - May scar due to length of healing time
- Herpetiform RAS
 - Small ulcers ranging from 1-3 mm occurring in clusters
 - As many as 100 ulcers can present at single time
 - Variant most likely to have frequent recurrences
 - Usually occur on nonkeratinized mucosa, but can appear anywhere
 - Name refers to herpes-like appearance only, as no herpes virus is identified
 - Heals without scarring in 7-14 days

Treatment

- Surgical approaches
 - Laser ablation
 - Shortens duration
- Drugs
 - Corticosteroids
 - Dapsone
 - Thalidomide
 - Generally confined to HIV-associated major aphthous-like ulcers

Prognosis

- Recurrences can occur sporadically for many years

MICROSCOPIC

Histologic Features

- No unique microscopic features
- Early lesions show ulceration with fibrinopurulent membrane
- Mixed inflammatory cell infiltrate beneath ulcer bed composed of lymphocytes, histiocytes, and neutrophils
- Increased vascularity

DIFFERENTIAL DIAGNOSIS

Behçet Disease (BD)

- Clinical features
 - Multisystem disorder involving ocular, mucocutaneous, cardiovascular, renal, and central nervous system
 - Not common disease in USA but more frequent in Mediterranean countries (1 in 10,000)
 - Male $>>$ female (16-24:1)
 - Disease usually presents in 3rd decade
 - Exact etiology unknown but considered to be immunodysregulation disease
 - Proposed triggers include bacterial, viral, as well as environmental allergens
 - HLA-B51 frequently associated
 - TNF- α levels elevated
 - Oral and genital ulcers and posterior uveitis are common symptoms
 - Oral ulcerations often presenting symptom
 - Oral ulcers similar to RAS in both appearance, number, location, and duration
 - Genital ulcers similar in appearance to oral lesions and occur in 75% of patients

- Cutaneous lesions include pustules, vesicles, folliculitis, acneiform eruptions, and pyoderma
 - Skin exhibits positive pathergy test, unique to BD
- Microscopic features
 - Similar to RAS, therefore diagnosis is based on clinical findings
 - Can observe leukocytoclastic vasculitis of small vessels
- Treatment of oral BD
 - Similar to RAS
 - Tetracycline mouthrinse is effective
- Prognosis
 - Clinical course variable, making predictions of long-term prognosis difficult
 - Disease more severe in men

Reiter Disease (Reactive Arthritis)

- Systemic disorder of unknown etiology
 - Most frequently seen in young men
 - Usually triggered by urogenital or enteric infections
 - Bacteria include *Shigella*, *Salmonella*, *Streptococcus*, *Mycoplasma*, *Chlamydia*, and *Yersinia*
 - Associated with HLA-B27
 - Common in context of HIV infection
- Clinical features
 - Oral lesions seen in < 20% of cases
 - Oral and oropharyngeal erythema and ulceration
 - Circinate lesions of tongue similar in appearance to geographic tongue
 - Circinate balanitis, conjunctivitis, iritis, arthritis, keratotic plaques, and pustules on soles and palms
- Microscopic features
 - Biopsy of oral ulcer nonspecific and similar to RAS
 - Biopsy of circinate area of tongue similar in appearance to geographic tongue or psoriasis
- Treatment
 - Nonsteroidal anti-inflammatory drugs
 - Useful in managing arthritic component
 - Immunosuppressive agents
 - Corticosteroids, azathioprine, methotrexate
 - Use is limited in HIV-positive patients
- Prognosis
 - 2/3 of patients have self-limited course
 - Can have chronic recurrent ocular inflammation

Crohn Disease (Regional Ileitis; Regional Enteritis)

- Idiopathic inflammatory disorder of gastrointestinal tract
 - Primarily affects proximal colon and distal portion of small bowel
 - Most likely immune-mediated disease
 - Genetic, microbial, environmental, dietary, and vascular factors have been implicated
 - Incidence in USA is 7/100,000 cases
 - Incidence increasing particularly in northern latitudes
 - More common in whites than blacks or Asians
 - 2-4x higher incidence in Jewish population
 - Female > male (1.2:1)
 - Age of onset is bimodal: 15-30 years, 60-80 years
 - Most cases diagnosed by age 30
- Clinical features
 - Oral lesions

- May be initial presentation of disease
- Aphthous-like ulcerations
- Diffuse or nodular swelling of oral and perioral tissues termed orofacial granulomatosis
- Patchy erythema of gingiva
- Microscopic features
 - Noncaseating granulomatous inflammation in superficial mucosa can be seen in oral biopsies
 - Feature can be variable
 - Special stains for organisms are **negative**
 - Nonspecific ulceration similar to RAS
- Treatment
 - Oral lesions may clear with treatment for gastrointestinal disease
 - Persistent oral ulcerations can be managed with topical corticosteroids
- Prognosis
 - Chronic disease with recurrent relapses

Traumatic Ulcerative Granuloma

- Histologically, inflammation extends much deeper into striated muscle
- Sheets of histiocytes and lymphocytes with scattered eosinophils are seen

Herpes Simplex Virus (HSV), Type 1

- Most HSV-1 ulcers occur on lip vermillion
- Intraoral HSV-1 usually presents on keratinized mucosa (hard palate, attached gingiva)
- Acantholytic epithelial cells are seen in ulcer (Tzanck cells)
 - Ballooning degeneration of infected cell with margination of chromatin
 - Infected cells can fuse to form multinucleated cells
- HSV1 in situ hybridization will be positive in infected cells
- Older HSV1-associated lesions are indistinguishable from RAS

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Painful oral ulcers ranging in size from 1 mm to > 1 cm
- Ulcers usually last 7-14 days
- Noninfectious etiology

Pathologic Interpretation Pearls

- Microscopic findings are of nonspecific ulcer
- Clinical correlation required to make diagnosis

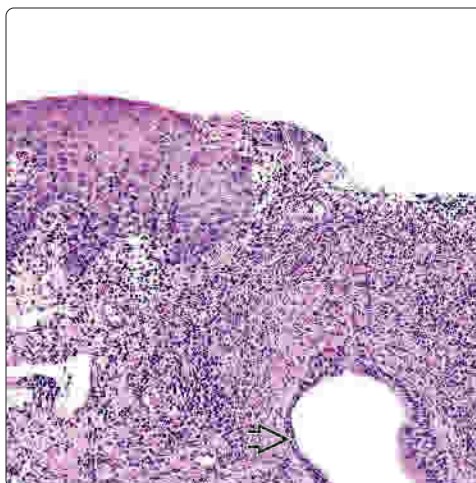
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Behçet Disease

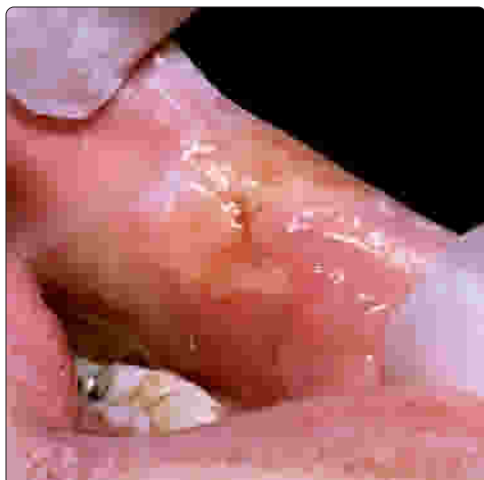


Behçet Disease Ulcer



(Left) Clinical photograph shows Behçet disease. Numerous ulcers 0.5 cm to > 1 cm are noted on both upper and lower lips. The ulcers of Behçet disease are indistinguishable from aphthous ulcers; therefore, the diagnosis is based on clinical and not pathologic findings. (Right) Biopsy of a lip ulcer from a patient with Behçet disease shows salivary gland ductal hyperplasia [B] adjacent to the inflammation. The microscopic findings are not unique and are similar to aphthous ulcers.

Reactive Arthritis

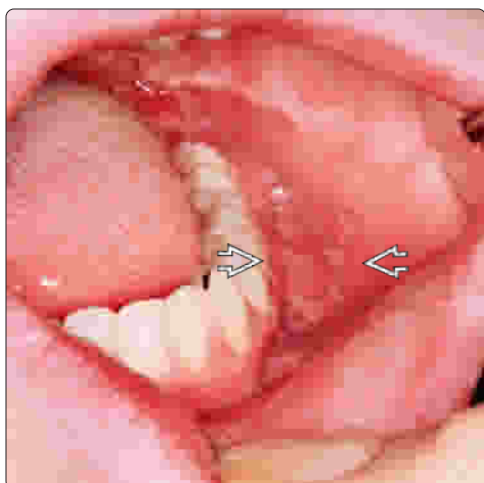


Lesions on Sole of Foot in Reactive Arthritis

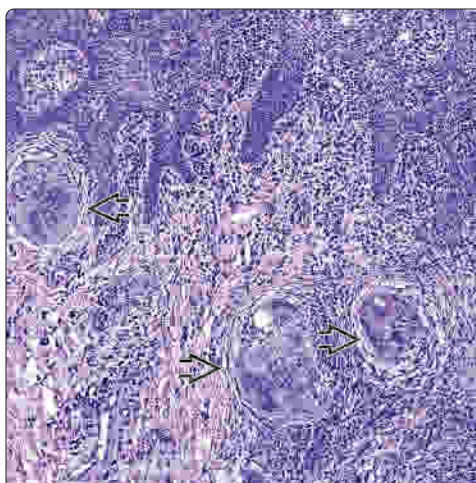


(Left) This clinical photograph is of a 27-year-old man with reactive arthritis (Reiter disease) presenting with large aphthous-like ulcerations, acute onset of arthritis, and keratotic plaques of the soles. Microscopic examination revealed a nonspecific ulcer similar to aphthous ulcers. (Right) Pustules and crusted papules on the soles of the same patient. Reactive arthritis usually follows a bout of urethritis or gastroenteritis.

Oral Manifestations of Crohn Disease



Histology of Oral Ulcer in Crohn Disease



(Left) A 15-year-old boy with a linear ulceration in the mandibular vestibule [B] is shown. Based on the biopsy results of the oral ulcer the patient underwent gastrointestinal work-up and was found to have Crohn disease. (Right) Oral biopsy from a patient with Crohn disease shows nonnecrotizing granulomatous inflammation in the superficial lamina propria [B]. Often granulomas are not seen in oral biopsy specimens.

Pemphigus Vulgaris

KEY FACTS

TERMINOLOGY

- Autoimmune mucocutaneous disease characterized by intraepithelial blistering

CLINICAL ISSUES

- Most common in 4th-6th decade
- Mucosal pemphigus vulgaris (PV) may be only manifestation of disease or precede cutaneous PV by average of 5 months
- Bullae &/or blisters that easily rupture, resulting in irregularly shaped, painful ulcers and erosions

MICROSCOPIC

- Suprabasal bullae formation with intraepithelial clefting
- Round, swollen, hyperchromatic acantholytic (Tzanck) cells in cleft spaces

ANCILLARY TESTS

- Exfoliative cytology specimens of blister will demonstrate acantholytic cells (Tzanck cells)

- Direct immunofluorescence (DIF) of perilesional tissue will show homogeneous staining of IgG in intercellular spaces
- Indirect immunofluorescence (IIF) using serum from PV patients with monkey esophagus substrate
- 80-90% of patients demonstrate circulating IgG antibodies against desmoglein 1 &/or 3

TOP DIFFERENTIAL DIAGNOSES

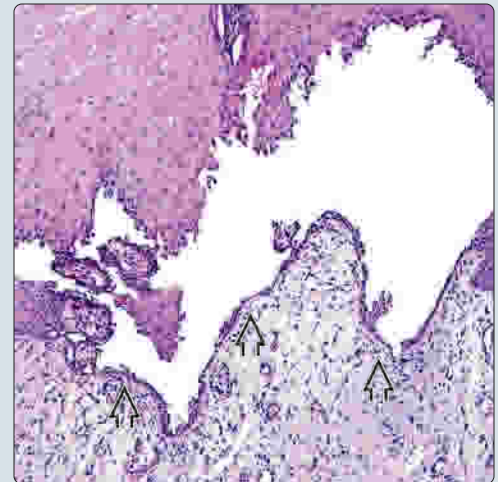
- Mucous membrane pemphigoid (MMP)
 - Blistering disease characterized by sub-basal separation of epithelium
- Paraneoplastic pemphigus
 - Can be distinguished from PV by DIF and IIF
- Erosive lichen planus
 - Sub-basal separation of epithelium with basal cell degeneration
- Erythema multiforme
 - Can be distinguished from PV by DIF

Clinical Presentation of Pemphigus Vulgaris

(Left) Clinical photo shows pemphigus vulgaris (PV) involving the buccal mucosa. The white areas represent collapsed bullae and the red areas are mucosal erosions which are characterized by ragged borders. This clinical finding shares similarities to mucous membrane pemphigoid and erosive lichen planus. (Right) Low-power view of PV illustrates the typical intraepithelial clefting just above the basal layer. A mild to moderate chronic inflammatory cell infiltrate may be present.

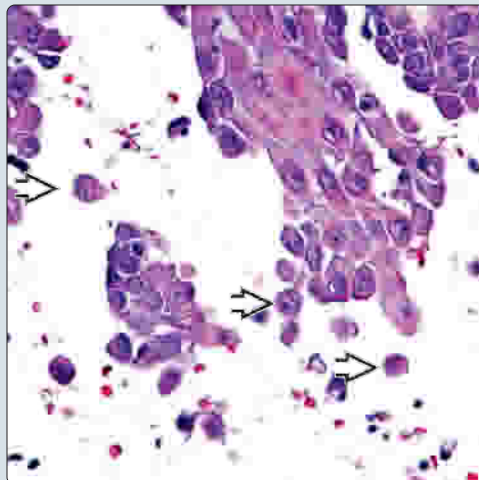


Suprabasal Clefting in Pemphigus Vulgaris



Tzanck Cells in Pemphigus Vulgaris

(Left) Round, swollen, acantholytic cells in the spinous layer (Tzanck cells) are often seen within the intraepithelial clefts in PV. The presence of these cells is helpful in making a diagnosis in an exfoliative cytologic preparation. (Right) DIF of perilesional skin in PV shows a characteristic fishnet pattern of IgG deposits in the intercellular desmosomal areas at all levels of the epidermis. Using patient serum, a similar pattern is present in indirect immunofluorescence.



Direct Immunofluorescence



TERMINOLOGY

Abbreviations

- Pemphigus vulgaris (PV)

Definitions

- Autoimmune mucocutaneous disease characterized by intraepithelial blistering

ETIOLOGY/PATHOGENESIS

Etiology

- Circulating autoantibodies to desmoglein 1 and 3 adhesion molecules of squamous epithelium
 - Inhibits cell-cell adhesion resulting in acantholysis and blister formation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Varies by geographic area and ethnic group
 - 0.76/million per year in Finland to 16/million per year in Israel
- Age
 - Most common in 4th-6th decade
- Sex
 - Equal sex distribution
- Ethnicity
 - Higher prevalence in Ashkenazi Jews and people of Mediterranean ancestry

Site

- Mucous membranes: Oral, nasal, esophagus, larynx, nasopharynx, conjunctivae, genitalia, anal mucosa
- Cutaneous sites mostly on intertriginous areas, trunk, head, and neck

Presentation

- Mucosal PV may be only manifestation of disease or precede cutaneous PV by average of 5 months
- Oral mucosal PV originates in 50-70% of patients
- Bullae &/or blisters that easily rupture, resulting in irregularly shaped, painful ulcers and erosions
- > 90% of patients will have oral involvement during disease course
- Positive Nikolsky sign and Asboe-Hansen sign

Natural History

- With treatment, complete remission has been reported, ranging from 2-10 years

Treatment

- Drugs
 - Local &/or systemic therapy based on disease severity
 - Systemic &/or topical corticosteroids
 - Adjuvant immunosuppressants used for steroid sparing effect
 - Plasmapheresis
 - High-dose IV IgG
 - Anti-inflammatory drugs
 - Rituximab

Prognosis

- Mortality reported in up to 6% of patients
 - Systemic infections most common cause of death

MICROSCOPIC

Histologic Features

- Suprabasal bullae formation with intraepithelial clefting
- Round, swollen, hyperchromatic acantholytic (Tzanck) cells in cleft spaces
- Irregular papillary projections of the submucosa lined by single row of basal cells with cuboidal shape
- Little or no inflammation during early bullous phase

ANCILLARY TESTS

Cytology

- Exfoliative cytology specimens of blister will demonstrate acantholytic cells (Tzanck cells)

Immunofluorescence

- Direct immunofluorescence (DIF) of perilesional tissue will show homogeneous staining of IgG in intercellular spaces
 - May also see complement component C3 or IgA
- Indirect immunofluorescence (IIF) using serum from PV patients with monkey esophagus substrate
 - 80-90% of patients demonstrate circulating IgG antibodies against desmoglein 1 &/or 3
 - Antibody titers correlate with disease activity

DIFFERENTIAL DIAGNOSIS

Mucous Membrane Pemphigoid (MMP)

- Blistering disease characterized by sub-basal separation of epithelium
- DIF shows linear band of IgG(A) at basement membrane zone

Paraneoplastic Pemphigus

- Histology can be similar to PV, MMP, or erythema multiforme
- Can be distinguished from PV by DIF and IIF

Erosive Lichen Planus

- Sub-basal separation of epithelium with basal cell degeneration

Erythema Multiforme

- Can be distinguished from PV by DIF

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Acantholysis with suprabasal separation
- Immunofluorescence required for definitive diagnosis

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Mucous Membrane Pemphigoid

KEY FACTS

TERMINOLOGY

- Chronic, blistering mucocutaneous autoimmune disease

CLINICAL ISSUES

- Incidence estimated to be between 1 in 12,000-20,000
- Generally presents in 6th or 7th decade
- Female > male (2:1)
- Gingival involvement seen in 64% of cases
- Ocular lesions occurs in up to 37% of patients with oral mucous membrane pemphigoid
- Esophageal involvement can result in esophageal stenosis from repeated untreated ulcers
- Laryngeal involvement uncommon but can affect vocal cords leading to dysphonia and hoarseness
- Nasal and nasopharyngeal involvement can cause epistaxis and mucosal scarring
- Chronic life-long disease with periods of remission

MICROSCOPIC

- Perilesional mucosa shows subepithelial clefting
- Direct immunofluorescence (DIF)
 - Shows continuous linear band IgG or C3 at basement membrane zone
 - Can also see IgM and IgA
- Indirect immunofluorescence
 - Salt-split skin can detect circulating antibodies to basement membrane zone
 - Not all patients have circulating antibodies

TOP DIFFERENTIAL DIAGNOSES

- Erosive lichen planus
 - Basal cell liquefaction with a band-like lymphocytic infiltrate
- Pemphigus vulgaris
 - Clinically similar but pathology shows suprabasal separation

Desquamative Gingivitis in Mucous Membrane Pemphigoid

(Left) Mucous membrane pemphigoid presents as desquamative gingivitis. The attached gingiva is erythematous and swollen. Oftentimes blisters form leaving painful denuded mucosa. This is one of the most common presentations. (Right) Mucous membrane pemphigoid with characteristic subepithelial clefting and intact basal cells shows a sparse inflammatory cell infiltrate in the superficial lamina propria.

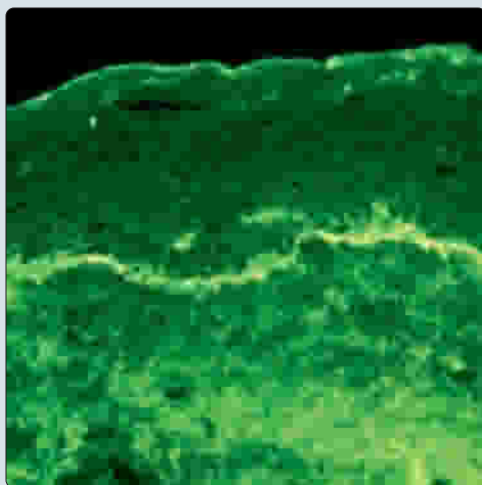


Subepithelial Clefting With Intact Basal Cells

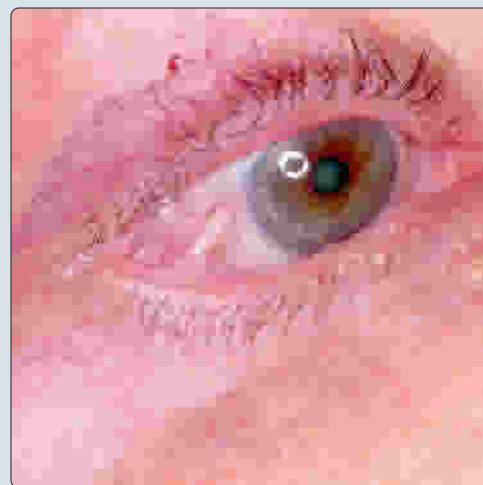


Mucous Membrane Pemphigoid Immunofluorescence

(Left) Direct immunofluorescence of perilesional mucosa from a patient with mucous membrane pemphigoid is shown. A continuous linear deposit of IgG at the basement membrane zone is observed. C3, IgA, and IgM may also be identified. (Right) Symblepharon formation is seen between the bulbar and palpebral conjunctivae from a mucous membrane pemphigoid patient with ocular involvement.



Symblepharon in Mucous Membrane Pemphigoid



TERMINOLOGY

Abbreviations

- Mucous membrane pemphigoid (MMP)

Synonyms

- Cicatricial pemphigoid, ocular cicatricial pemphigoid

Definitions

- Chronic, heterogenous group of subepithelial blistering mucocutaneous autoimmune diseases

ETIOLOGY/PATHOGENESIS

Unknown

- Some studies show antibodies specific for hemidesmosomal antibodies BPAG1 or BPAG2
- Some patients have antibodies to $\beta 4$ integrin subunit, laminin 5 and 6, and other antigens with unknown identity
- In USA, MMP associated with *HLA-DQB1*0301*
- Possible medications triggers include methylodopa and clonidine

CLINICAL ISSUES

Epidemiology

- Incidence estimated to be between 1 in 12,000-20,000
- Generally presents in 6th or 7th decade
- Female > male (2:1)

Presentation

- Oral lesions
 - Vesicles or blisters on mucosa that erupt, leaving raw area
 - Positive Nikolsky sign (induced trauma can elicit blister on clinically normal mucosa)
 - Gingival involvement seen in 64% of cases presenting as desquamative gingivitis
 - Also seen on buccal mucosa, palate, alveolus, tongue, and lower lip
- Ocular lesions
 - Occur in up to 37% of patients with oral MMP
 - Chronic conjunctival irritation
 - Conjunctival ulcers develop with subsequent scarring
 - Adhesions (symblepharons) develop that fuse scleral and palpebral conjunctiva
 - As disease progresses, entropion formation causes eyelashes to rub against cornea
- Upper aerodigestive tract
 - Esophageal involvement can result in esophageal stenosis from repeated untreated ulcers
 - Laryngeal involvement uncommon but can affect vocal cords leading to dysphonia and hoarseness
 - Nasal and nasopharyngeal involvement can cause epistaxis and mucosal scarring
- Other sites
 - Anus, rectum, and vagina can be affected
 - Cutaneous involvement reported in 10-43%

Treatment

- Surgical approaches
 - In ocular lesions, surgery to ablate ingrown eyelashes and release entropions

- Esophageal strictures may require dilatation
- Laryngeal stenosis may require tracheostomy
- Medical approaches
 - Corticosteroids, both topical and systemic
 - Steroid-sparing therapy: Dapsone, cyclophosphamide, azathioprine, cyclosporine, and methotrexate
 - Intravenous Ig therapy
 - Anti-inflammatory drugs: Tetracycline
 - Rituximab, often in combination with IVIg therapy

Prognosis

- Chronic life-long disease with periods of remission

MICROSCOPIC

Histologic Features

- Perilesional mucosa shows subepithelial clefting
- Sparse inflammatory cell infiltrate, usually lymphocytes and plasma cells

Immunopathology

- Direct immunofluorescence (DIF)
 - Continuous linear band at basement membrane zone of fixed IgG or complement (C3)
 - Can also see IgM and IgA
- Indirect immunofluorescence
 - Salt-split skin can detect circulating antibodies to basement membrane zone
 - Not all patients have circulating antibodies
 - Antibody titer does not correlate with disease activity

DIFFERENTIAL DIAGNOSIS

Erosive Lichen Planus

- May share clinical and histologic features, but DIF will distinguish the 2 entities

Pemphigus Vulgaris

- Clinically similar but suprabasal separation seen

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Gingival involvement almost universal
- Ocular involvement results in scarring

Pathologic Interpretation Pearls

- Subepithelial clefting with sparse inflammation in superficial lamina propria
- DIF shows continuous linear band of IgG and C3 at basement membrane zone

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KEY FACTS

TERMINOLOGY

- Chronic, self-limited, inflammatory disorder that involves mucous membranes, skin, nails, and hair

CLINICAL ISSUES

- Between 0.5-2%
- Peaks in middle-aged adults
- Reticular lichen planus (LP) usually asymptomatic
- Erosive LP exhibits atrophic erythematous mucosa with ulcerations

MICROSCOPIC

- Varying degrees of ortho- or parakeratosis
- Rete ridges can demonstrate sawtooth pattern
- Basal cell layer exhibits liquefaction (hydropic degeneration)
- Band-like, predominately T lymphocytes adjacent to basement membrane
- Ulceration or sub-basal separation seen in erosive LP

- Direct immunofluorescence of perilesional tissue not specific or diagnostic
- No significant atypia should be seen

TOP DIFFERENTIAL DIAGNOSES

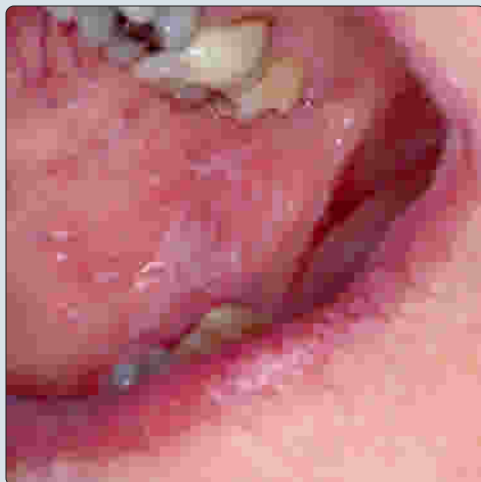
- Mucous membrane pemphigoid
- Lichenoid reaction to dental amalgam
- Lichenoid reaction to drugs and topical agents
- Cinnamon-induced stomatitis
- Lupus erythematosus
- Oral dysplasia

DIAGNOSTIC CHECKLIST

- Oral LP should be multifocal
- Sub-basal separation of epithelium from connective tissue
- Lichenoid lesions with dysplasia should not be diagnosed as LP with dysplasia
- Multiple lichenoid lesions with varying degrees of dysplasia may represent proliferative verrucous leukoplakia

Reticular Lichen Planus

(Left) Reticular variant of oral lichen planus of the buccal mucosa is shown, characterized by white papules and lace-like reticulations. These lesions are generally bilateral and affect other sites in the oral cavity. **(Right)** Lichen planus of oral mucosa often shows acanthosis and sawtooth rete ridges. A band-like lymphocytic infiltrate is seen adjacent to the basement membrane with basal cell degeneration.

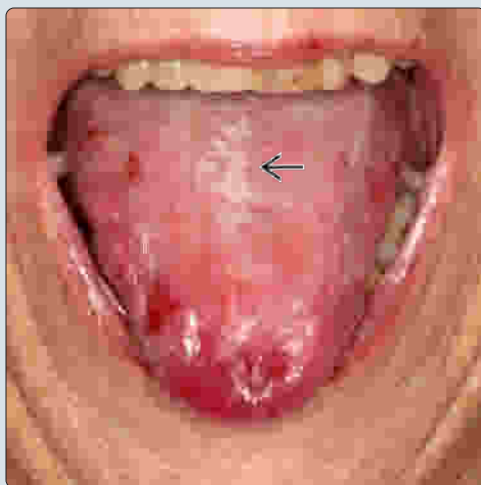


Sawtooth Rete in Lichen Planus

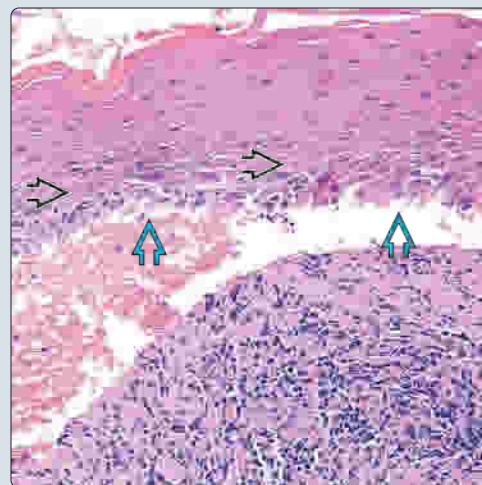


Erosive Lichen Planus

(Left) Dorsal tongue lichen planus generally presents with thickened white plaques [E]. Note the erythema, erosions, and ulcers on the dorsolateral and tip of tongue. **(Right)** Basal cell degeneration [E] is the hallmark of lichen planus and leads to a subepithelial separation from the underlying connective tissue. The resulting ulcer from the separation clinically presents as erosions and is highly symptomatic. Cytoid bodies [E] are usually noted near the epithelial-connective tissue interface.



Subepithelial Separation With Basal Cell Degeneration



TERMINOLOGY

Abbreviations

- Lichen planus (LP)

Definitions

- Chronic, self-limited, inflammatory disorder that involves mucous membranes, skin, nails, and hair

ETIOLOGY/PATHOGENESIS

Etiology

- Precise cause unknown

Pathogenesis

- Thought to be T-cell immune-mediated response
 - Activated CD8(+) T cells trigger basal cell apoptosis
 - Exact mechanism unknown and may involve mast cell chemotaxis or matrix metalloproteinases disrupting basement membrane
- No HLA association found
- Drug reactions
 - Many drugs have been reported to be associated with onset of LP
- Hepatitis C (HCV)
 - Association is controversial

CLINICAL ISSUES

Epidemiology

- Incidence
 - 0.5-2% of general population
- Age
 - Peaks in middle-aged adults
- Sex
 - Female > male (3:2)

Site

- Oral LP most commonly involves buccal mucosa (90%)
- Gingiva, dorsal tongue, and lower lip also commonly involved by LP
 - Approximately 10% of patients have LP confined to gingiva
- Uncommon sites include palate and upper lip

Presentation

- **Reticular LP**
 - ~ 23% of oral cases
 - Usually asymptomatic
 - Lesions involve multiple sites
 - Fine white lace-like striae (Wickham striae) on buccal mucosa, gingiva, and lip
 - White plaques on dorsal tongue
 - ~ 44% of oral LP patients will develop cutaneous LP
 - Scalp and nail involvement rare in patients with only oral LP
- **Erythematous LP**
 - ~ 40% of oral cases
 - Atrophic erythematous mucosa with ulcerations
 - Periphery of lesion will show features of reticular LP
- **Erosive LP**
 - ~ 37% of oral cases

- Can be confined to gingiva
 - LP confined to gingiva and genitals is recognized; more common in females

Bullous LP

- Unusual variant where bullae are formed
- Positive Nikolsky sign can be elicited
- Multiple morphologies may present simultaneously
 - Predominant morphology may change over time
 - More severe forms (erythematous/erosive) can be seen in older patients

Treatment

- Adjuvant therapy
 - **Reticular LP**
 - No treatment is needed
 - **Erosive LP**
 - Topical or systemic corticosteroids
 - Topical cyclosporine
 - Tacrolimus has been used for steroid resistant LP

Prognosis

- Chronic disease
 - Symptoms wax and wane over patient lifetime
 - Rarely undergoes spontaneous remission
- Malignant transformation
 - Controversial: Some cases not confirmed as LP histologically
 - Documented cases occur in atrophic or chronic ulcerative areas
 - Long-term clinical follow-up recommended for erosive LP

MICROSCOPIC

Histologic Features

- Varying degrees of orthokeratosis or parakeratosis
- Both atrophy and acanthosis can be seen
- Rete ridges can demonstrate sawtooth pattern
- Basal cell layer exhibits vacuolar change
- Degenerating keratinocytes (Civatte, hyaline, or colloid bodies) are noted at epithelial-connective tissue interface
- Band-like, predominately T lymphocytes adjacent to basement membrane
 - Plasma cells can also be present
 - More common from biopsies of gingival LP
- Ulceration or sub-basal separation seen in erosive LP
- No significant atypia should be seen
 - Superimposed candidiasis may cause reactive atypia

Immunopathology

- Direct immunofluorescence (DIF) of perilesional tissue
 - Not specific or diagnostic
 - May show linear or granular deposits of fibrin or fibrinogen and colloid bodies
 - Deposits of C3, IgM, IgG, and IgA occasionally seen

DIFFERENTIAL DIAGNOSIS

Mucous Membrane Pemphigoid

- Immunopathology useful in delineating disease from LP
 - DIF shows continuous linear band at basement membrane zone of fixed IgG and C3

Causative Agents in Oral Lichenoid Reactions

Oral Lichenoid Drug Reactions	Oral Lichenoid Contact Reactions
Antihypertensives	Dental materials
Propranolol	Mercury
Hydrochlorothiazide	Nickel
Spirolactone	Palladium
Antimalarials	Silver
Chloroquine	Gold
Quinidine	Pallidum
Quinolone	Bismuth
Antibiotics	Glass Ionomer
Tetracycline	Composite
Ketoconazole	Porcelain
Nonsteroidal anti-inflammatory drugs	Flavoring agents
Naproxen	Cinnamon (cinnamic aldehyde)
Ibuprofen	Mint (Mentha piperita)
Diclofenac	Tartar-control toothpaste
Miscellaneous	Eugenol
Gold	Balsam of Peru
Palladium	Dental adhesives
Penicillamine	Acrylate compounds
Allopurinol	Eugenol

Lichenoid Reaction to Dental Amalgam

- Noted where there is direct contact of mucosa with dental amalgam
- Often lymphocytic infiltrate forms tertiary lymphoid follicles

Lichenoid Reaction to Drugs

- Seen in association with many systemic medications
- May see more diffuse pattern of inflammation, including perivascular

Lupus Erythematosus

- Superficial and deep perivascular inflammatory infiltrate
- Immunopathology not specific

Cinnamon-Induced Stomatitis

- Acanthosis with neutrophilic exocytosis
- Mixed inflammation in superficial lamina propria
- Marked interface change

Chronic Graft-vs.-Host Disease

- Epithelium exhibits basal cell liquefaction with numerous dyskeratotic keratinocytes
- Patchy moderate lymphocytic infiltrate in submucosa
- Diagnosis based on clinical history
 - Lesions present on average 6 months post transplantation

Oral Dysplasia

- Can see intense inflammatory cell infiltrate mimicking LP
- Dyskeratotic epithelial cells can be noted
- Dysplasia that cannot be attributed to infection or ulceration

Pemphigus Vulgaris

- Suprabasilar separation of epithelium

Chronic Ulcerative Stomatitis

- Clinically similar to LP
- DIF shows speckled or granular perinuclear IgG in lower 1/3 of epithelium

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Oral LP should be multifocal
 - Solitary lesions may represent lichenoid keratoses

Pathologic Interpretation Pearls

- Reticular LP exhibits the classic histology of LP
 - Reactive changes and mixed inflammation can be noted in erosive LP
- No significant dysplasia should be seen
 - Lichenoid lesions with dysplasia should not be diagnosed as LP with dysplasia; most likely represents proliferative verrucous leukoplakia

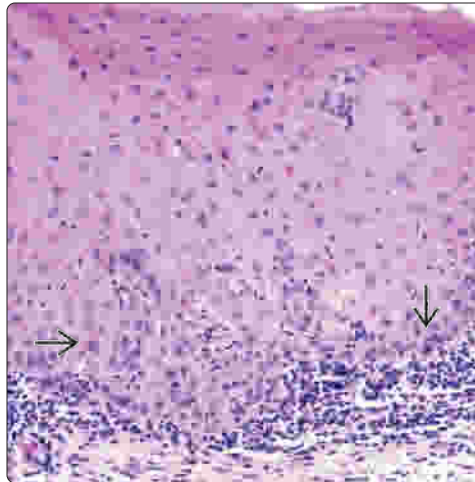
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Lichen Planus Presenting as Desquamative Gingivitis

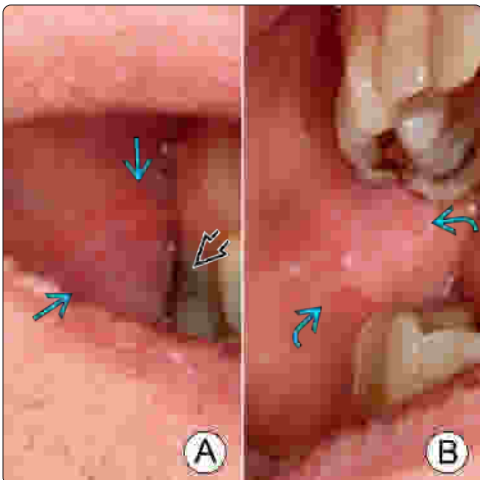


Basal Cell Hydropic Degeneration



(Left) Erosive lichen planus presents as desquamative gingivitis. When this is the only clinical finding, it is difficult to distinguish from mucous membrane pemphigoid or pemphigus vulgaris, and biopsy confirmation is required for diagnosis. (Right) High-power photomicrograph shows hydropic degeneration of the basal cells. Civatte or colloid bodies are scattered at the epithelium-connective tissue interface. Inflammatory cell exocytosis is noted.

Oral Lichenoid Contact Reaction to Amalgam

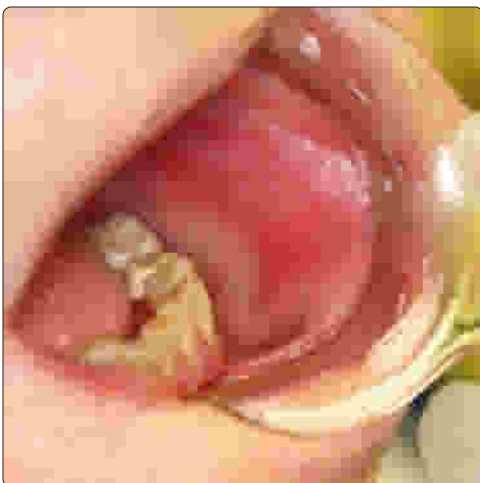


Tertiary Lymphoid Follicle in Lichenoid Reaction to Amalgam

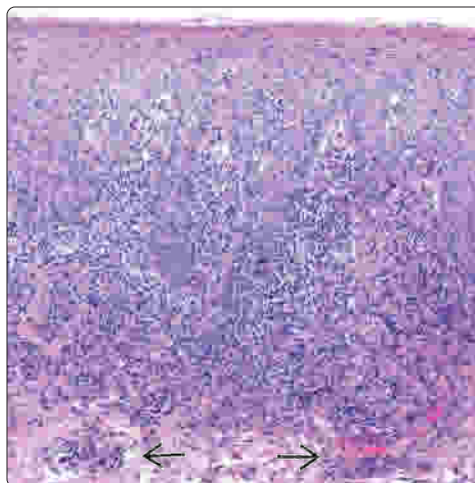


(Left) A) Oral lichenoid contact reaction to a large amalgam restoration on the buccal aspect of a maxillary molar is shown with direct contact of the amalgam to the affected mucosa. B) The mucosa presents as areas of erythema and white plaques. (Right) The epithelium is atrophic and a dense lymphocytic infiltrate is seen in the lamina propria in this case of lichenoid reaction to dental amalgam. Numerous tertiary lymphoid follicles are present as well as perivascular inflammation.

Oral Lichenoid Contact Reaction to Cinnamon



Epithelial Acanthosis and Elongated Rete



(Left) A large area of erythema is shown on the buccal mucosa in a patient who would hold cinnamon chewing gum in this location for many hours each day. The mucosa was sensitive to spicy and acidic foods. These lesions completely resolved upon cessation of the product. (Right) Marked acanthosis and inflammatory cell exocytosis is present in this case of cinnamon stomatitis. The inflammatory infiltrate in the submucosa is more mixed than in LP. Perivascular inflammation is frequently seen.

KEY FACTS

TERMINOLOGY

- Acute, immune-mediated, self-limiting mucocutaneous inflammatory disease

ETIOLOGY/PATHOGENESIS

- Most cases associated with T-cell mediated immune reaction to precipitating agent
- 90% of cases associate with infectious agent, most commonly herpes simplex virus (HSV) type 1 (although HSV type 2 can also induce erythema multiforme [EM]) and *Mycoplasma pneumoniae*
- Drug-associated EM accounts for < 10% of cases; most commonly reported medications are NSAIDs, sulfonamides, antiepileptics, and antibiotics

CLINICAL ISSUES

- EM minor: Skin target lesions with only 1 mucous membrane site affected
- Lip > buccal mucosa > labial mucosa > tongue > soft palate

- Lip shows characteristic hemorrhagic crusting
- Target or bull's-eye lesions of skin are hallmark of EM
- Self-limiting disease ranging from 2-6 weeks
- Subset of patients experience recurrent EM (20%)

MICROSCOPIC

- Early: Upper lamina propria edema and blisters
- Mixed inflammatory cell infiltrate
- Hydropic degeneration of basal cells
- Individually necrotic keratinocytes within epithelium

ANCILLARY TESTS

- IgM and C3 are found along basement membrane zone and in walls of blood vessels

TOP DIFFERENTIAL DIAGNOSES

- Primary herpes stomatitis, pemphigus vulgaris, mucous membrane pemphigoid, Behçet disease

(Left) Erythema multiforme involving the lips shows a large area of ulceration and hemorrhage that eventually form characteristic crusts. The lips are the most common site of oral involvement. This appearance in the absence of skin lesions is nondiagnostic and can overlap with other ulcerative diseases. (Right) Typical target or bull's-eye skin lesions are the hallmark of erythema multiforme. The most common sites are extremities with symmetrical involvement.

Lip Crusting

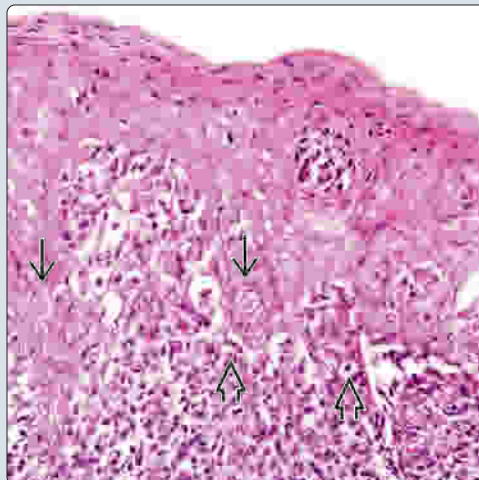


Target Lesion

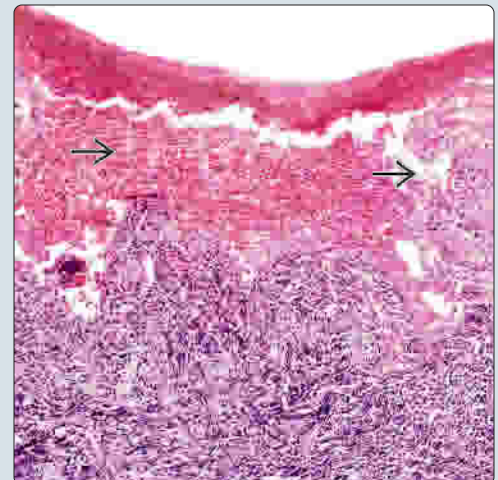


(Left) Vacuolar interface change at the epithelial-stromal junction, along with hydropic changes of basal cells with dyskeratosis, are typical of early erythema multiforme. Inflammation may be variable. (Right) This older lesion of erythema multiforme displays partial to full thickness necrosis along with a moderate inflammatory cell infiltrate.

Early Lesion of Erythema Multiforme



Erythema Multiforme



TERMINOLOGY

Abbreviations

- Erythema multiforme (EM)

Definitions

- Acute, immune-mediated, self-limiting mucocutaneous inflammatory disease

ETIOLOGY/PATHOGENESIS

Immune Reaction

- Most cases associated with T-cell mediated immune reaction to precipitating agent
 - 90% of cases associate with infectious agent, most commonly herpes simplex virus (HSV) type 1 (although HSV type 2 can also induce EM) and *Mycoplasma pneumoniae*
 - Drug-associated EM accounts for < 10% of cases; most commonly reported medications are NSAIDs, sulfonamides, antiepileptics, and antibiotics

Genetic Susceptibility

- HLA-DQB1*0301 allele found in patients with HSV-associated EM
- HLA-B35, HLA-B62, and HLA-DR-53 associated with recurrent EM

CLINICAL ISSUES

Epidemiology

- Age
 - Peak: 20-40 years
 - 20% of cases reported in children

Site

- Primarily associated with target lesions of skin with involvement of no more than 1 mucous membrane (usually oral)

Presentation

- Mucous membrane involvement, when present, is confined to 1 site
 - Oral involvement
 - Lip > buccal mucosa > labial mucosa > tongue > soft palate
 - Lip shows characteristic hemorrhagic crusting
- Target or bull's-eye lesions of extremity skin are hallmarks of EM
 - Begin as dusky red flat macules or papules with regular round shape < 3 cm

Natural History

- Self-limiting disease ranging from 2-6 weeks
- Subset of patients experience recurrent EM (20%)

Treatment

- Options, risks, complications
 - Offending agent, if known, should be stopped
 - Symptomatic treatment with analgesics
- Drugs
 - Herpes-associated EM can be treated with antiviral medication

- Often used prophylactically in herpes-associated recurrent erythema multiforme

- Cyclosporine, levamisole, dapsone, and cyclophosphamide used in severe outbreaks
- Systemic corticosteroid commonly used

Prognosis

- Self-limiting disease

MICROSCOPIC

Histologic Features

- Early lesions present with edema in upper lamina propria resulting in blister formation
 - May form both intra- and subepithelial blisters
- Mixed inflammatory cell infiltrate of lymphocytes, neutrophils, and occasionally, eosinophils
 - Perivascular location and in superficial lamina propria
- Inflammatory cell exocytosis with spongiosis and intracellular edema of epithelium
- Hydropic degeneration of basal cells
- Individually necrotic keratinocytes scattered throughout epithelium

ANCILLARY TESTS

Immunofluorescence

- IgM and C3 are found along basement membrane zone and in walls of blood vessels

DIFFERENTIAL DIAGNOSIS

Primary Herpes Stomatitis

- In absence of cutaneous lesions, diagnosis may be difficult
 - Gingiva often involved in primary herpes but not in erythema multiforme

Pemphigus Vulgaris

- Chronic mucocutaneous disease of older patients
- Direct immunofluorescence diagnostic

Mucous Membrane Pemphigoid

- Chronic disease of older patients
- Subepithelial separation without neutrophils
- Direct immunofluorescence of IgG(A) along basement membrane

Behçet Disease

- No cutaneous lesions

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Pathology relatively nonspecific and requires clinical correlation

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KEY FACTS

TERMINOLOGY

- Autoimmune disease affecting connective tissues and multiple organs divided into 3 major categories
 - Systemic lupus erythematosus (LE) involves multiple organs with variety of cutaneous and oral manifestations
 - Chronic cutaneous LE or discoid lupus consists primarily of cutaneous and oral manifestations
 - Subacute cutaneous LE overlaps systemic LE and chronic cutaneous LE

ETIOLOGY/PATHOGENESIS

- Unknown; however, circulating autoantibodies directed against double stranded (ds)DNA, histones and nucleosomes are hallmark of SLE
- Parental history of SLE associated with > 14x increased risk of SLE in offspring

CLINICAL ISSUES

- Female > > male (5-10:1)

- Black > > white (1:250 vs. 1:1,000)

MICROSCOPIC

- Histology can vary depending on age of lesion
- Dermal edema with reticular mucin accumulation
- Hyperkeratosis with follicular plugging
- Superficial and deep perivascular and periadnexal infiltrate
- Incontinent melanin pigment in dermis
- Lymphocyte-rich interface dermatitis

ANCILLARY TESTS

- Direct immunofluorescence of lesional tissue in SLE and CCLE shows granular or shaggy deposits of IgG, IgM, (rare cases of IgA) or C3 at basement membrane zone

DIAGNOSTIC CHECKLIST

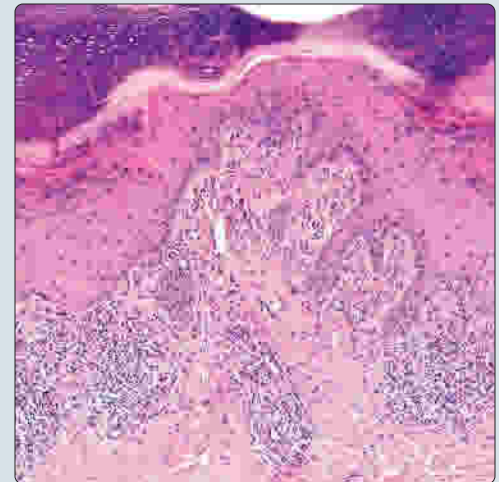
- Diagnosis based on correlation of clinical findings with serological and pathologic findings
- Microscopic features overlap with many other diseases and are not specific

Discoid Lupus Erythematosus

(Left) Chronic cutaneous (discoid) lupus occurring on the face is seen. The lesions often spread centrifugally with dilation of the follicle with a keratinous plug. Atrophy and scarring in older lesions is visible. **(Right)** Low-power image of hypertrophic chronic cutaneous (discoid) lupus erythematosus is shown. A patchy inflammatory cell infiltrate is seen with a superficial and deep perivascular pattern composed of lymphocytes and plasma cells. The band-like lymphocytic infiltrate of lichen planus is not seen.



Hypertrophic Discoid Lupus Erythematosus

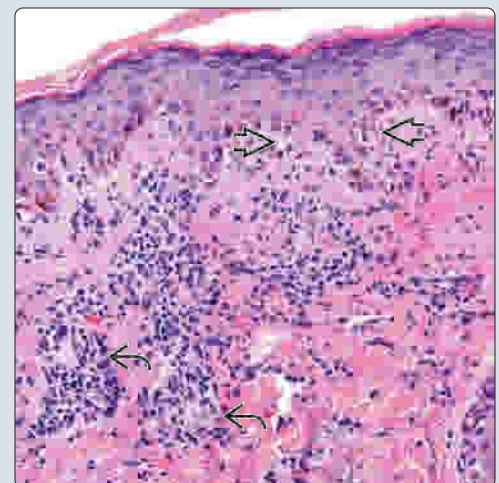


Radiating Striae of Oral Lupus Erythematosus

(Left) Intraoral systemic lupus erythematosus (SLE) presents as a central erosive area surrounded by radiating keratotic striae mimicking lichen planus. SLE can also have a nonspecific presentation. **(Right)** Biopsy specimen of an oral lesion in a patient with SLE demonstrates vacuolar degeneration of the basal cells as well as melanin pigment in basal cells. There is deeper lamina propria perivascular inflammation.



Oral Lupus Erythematosus



TERMINOLOGY

Abbreviations

- Lupus erythematosus (LE)
- Systemic lupus erythematosus (SLE)

Definitions

- Autoimmune disease affecting connective tissues and multiple organs divided into 3 major categories
 - SLE involves multiple organs with variety of cutaneous and oral manifestations
 - Chronic cutaneous LE (CCLE) or chronic discoid lupus consists primarily of cutaneous and oral manifestations
 - Subacute cutaneous LE (SCLE) has clinical features of both SLE and CCLE
- Neonatal lupus is secondary to maternal antibodies

ETIOLOGY/PATHOGENESIS

Etiology

- Unknown; however, circulating autoantibodies directed against double-stranded (ds)DNA, histones, and nucleosomes are hallmark of SLE
 - Type III hypersensitivity reaction
 - Local deposition of antinuclear antibodies in complex with released chromatin activates complement system, inducing serious inflammatory conditions
- Parental history of SLE associated with > 14x increased risk of SLE in offspring
- Drug-induced lupus reported
 - Procainamide, quinidine, and hydralazine have been associated with drug-induced lupus
 - Symptoms of lupus often resolve when inciting agent is removed
 - Lupus-like symptoms generally milder
 - Unlike SLE, male:female ratio equal and affects older individuals
- Ultraviolet light may precipitate or aggravate LE
 - Sun exposure can induce and exacerbate skin manifestations in cutaneous LE with time lag of up to 21 days

CLINICAL ISSUES

Epidemiology

- Incidence
 - Incidence in United States ranges from 2-7.6 cases per 100,000 population
 - ~ 16,000 new cases reported each year in USA
- Age
 - Range: 15-40 years
 - Mean: 30 years
- Sex
 - Female > > > male (5-10:1)
- Ethnicity
 - Black > > white (1:250 vs. 1:1,000)
 - Asian, Hispanic, and Native Americans are reported to have higher rate of lupus

Presentation

- SLE
 - Fatigue, myalgia, and joint pain

- Common findings affecting up to 95% of patients
- Mucocutaneous lesions in up to 85% of patients
 - Butterfly rash (malar region and nose bridge) in 40-50% of affected patients
 - Oral ulcers
 - Discoid rash
- Hematologic symptoms present in up to 85% of patients
 - Anemia
 - Leukopenia (< 4000/ μ L)
 - Lymphopenia (< 1000/ μ L)
- Kidney affected in 30-50% of patients
 - Lupus nephritis and uremia are serious complications
- Cardiopulmonary symptoms
 - Pericarditis most common complication
- Neuropsychiatric syndromes
 - Central nervous system
 - ◻ Aseptic meningitis
 - ◻ Cerebrovascular disease
 - ◻ Headache (migraine and benign intracranial hypertension)
 - Peripheral nervous system
 - ◻ Acute inflammatory demyelinating polyradiculoneuropathy
 - ◻ Guillain-Barre syndrome
- Raynaud phenomenon
- CCLE
 - Cutaneous lesions are scaly, erythematous patches that heal with scarring and hypo- or hyperpigmentation
 - Mostly affect face, particularly bridge of nose and malar area
 - Lesions tend to spread centrifugally
 - Follicular plugging and pigmentary changes are noted
 - ~ 50% of lesions present on hair-bearing areas of scalp or beard
 - Localized variant usually confined to head and neck region
 - Often this is only manifestation of LE
 - Oral lesions clinically resemble erosive lichen planus
 - Rarely present without cutaneous lesions
 - Patients with generalized CCLE involving areas below neck have higher risk of developing SLE
- SCLE
 - Cutaneous lesions predominately on trunk and arms (80%)
 - Symmetrical distribution on sun-exposed areas
 - Mild systemic disease, usually arthralgia
 - Renal disease uncommon
 - Lesions on face and scalp occur in 20% of patients
 - Lesions usually heal without scarring
 - Hyper- or hypopigmentations may be seen

Laboratory Tests

- SLE
 - Positive ANA
 - Positive anti-dsDNA (except ELISA) on ≥ 2 occasions
 - Positive anti-Sm
 - Antiphospholipid antibodies
 - anti- β 2 glycoprotein 1 IgG and IgA
 - Proteinuria > 0.5g/24 hour or 3+, nephritic syndrome, cellular casts

- Hemolytic anemia with reticulocytosis
- Low complement (C3, C4, or CH50)
- Positive Coombs test in absence of hemolytic anemia
- **CLE**
 - If direct immunofluorescence (DIF) and histology suggest LE, laboratory studies recommended
 - 25-80% of patients have positive ANA depending on sensitivity of test used
- **SCLE**
 - Most patients have positive ANA
 - Anti-Ro/SSA and anti-La/SSB antibodies

Treatment

- Avoid excessive sunlight exposure since UV light may precipitate disease
- Systemic corticosteroids in combination with immunosuppressive drugs for more severe disease
- Topical steroids effective for both cutaneous and oral lesions
- NSAIDs and antimalarials are effective for mild disease

Prognosis

- Prognosis of SLE depends on disease severity and which organs are involved
 - Renal failure most common cause of death
 - Chronic immunosuppression increases mortality due to infection and risk of malignancy

MICROSCOPIC

Histologic Features

- **SLE**
 - Pauci-inflammatory cell interface dermatitis
 - Dermal edema with reticular mucin accumulation
 - Normal basement membrane zone
- **CLE**
 - Ortho- and parakeratosis with follicular plugging
 - Basement membrane thickening with PAS(+) material
 - Subepithelial edema
 - Vacuolar degeneration of cells at dermoepidermal junction or basal cells of oral mucosa
 - Necrotic keratinocytes in basal and parabasal layer
 - Lymphocyte rich interface dermatitis
 - Predominately T cells
 - Superficial and deep perivascular and periadnexal lymphocytic infiltrate
 - Perineural lymphocytic infiltrate
 - Any lymphocytic aggregate encircling at least 1 nerve twig
 - Dermal fibrosis
 - Incontinent melanin pigment in dermis
 - Histology can vary depending on age of lesion
- **SCLE**
 - Suprabasilar exocytosis of inflammatory cells
 - Mild to moderate inflammation in superficial dermis

ANCILLARY TESTS

Immunofluorescence

- DIF of lesional tissue in SLE and CLE
 - Granular or shaggy deposits of IgG, IgM, (rare cases of IgA) or C3 at basement membrane zone

- Lupus band test (DIF) of normal uninvolved tissue is usually **positive** in SLE but not in CLE
 - Not specific to SLE and can be seen in Sjögren syndrome, rheumatoid arthritis, and systemic sclerosis

DIFFERENTIAL DIAGNOSIS

Oral Lichen Planus

- Can see similar pathology to LE and requires clinical and laboratory correlation
- Perivascular inflammation uncommon
- Subepithelial edema lacking
- No PAS(+) material in basement membrane zone
- DIF useful in differentiating these lesions

Drug Reaction

- Usually do not see dermal mucinosis, which is highlighted by Alcian blue-PAS staining
- Eosinophils, which are uncommon in LE, are usually seen

Rosacea

- Overlaps with cutaneous LE
- Follicular plugging uncommon in rosacea
- Usually do not see perineural lymphocytic infiltrate
- Sebaceous hyperplasia more common
- Demodex infestation more common
- Usually do not see dermal mucinosis, which is highlighted by Alcian blue
- No PAS(+) material in basement membrane zone

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Diagnosis based on correlation of clinical findings with serological and pathologic findings

Pathologic Interpretation Pearls

- Microscopic features overlap with many other diseases and are not specific

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Scarring Alopecia

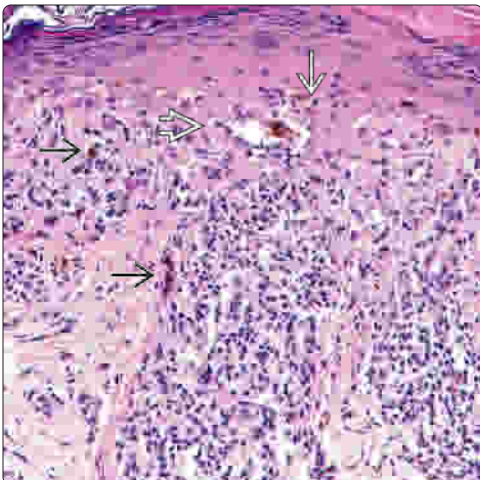


Cutaneous Lupus Erythematosus

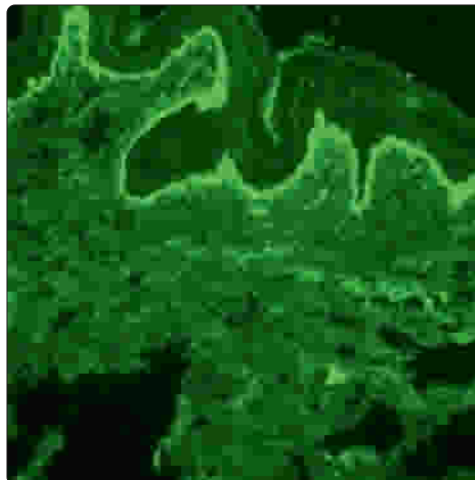


(Left) Cicatricial scarring alopecia in a patient with chronic cutaneous discoid lupus with both hyper- and hypopigmentation shows fibrotic scarring and a depressed central atrophic area. **(Right)** A biopsy of lupus erythematosus of the face with atrophic epidermis and keratotic plugging of the hair follicle shows a periappendiceal chronic inflammatory cell infiltrate in the dermis. Note increased dermal edema.

Interface Dermatitis With Vacuolar Changes

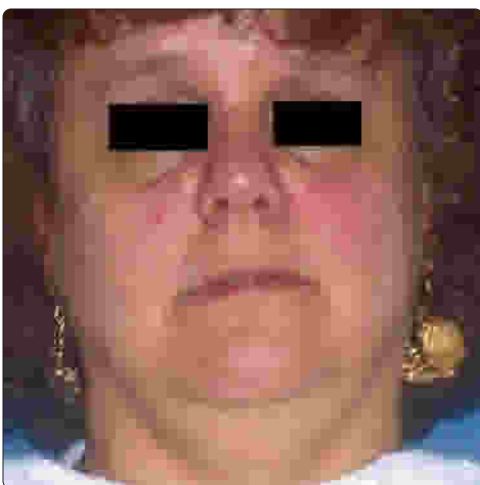


Direct Immunofluorescence

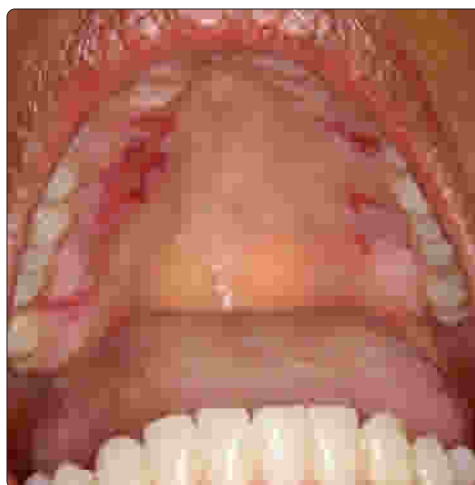


(Left) High-power photomicrograph of lupus erythematosus shows prominent interface dermatitis with vacuolar change and a superficial and deep perivascular infiltrate. Degenerating keratinocytes and suprabasilar exocytosis are present. Older lesions often show pigment incontinence in the dermis. **(Right)** Direct immunofluorescence of lesional tissue in lupus erythematosus shows a shaggy deposition of IgM at the basement membrane zone.

Butterfly Rash



Palatal Ulcers in Systemic Lupus Erythematosus



(Left) In 40-50% of affected patients with SLE, a malar rash presenting as an area of redness involving the bridge of the nose and the cheeks develops. The nasolabial folds are typically spared and sunlight worsens the condition. **(Right)** Irregularly shaped ulcers are present bilaterally on the hard palate. Areas of keratosis are present surrounding the ulcer. This clinical picture can mimic erosive lichen planus.

Traumatic Ulcerative Granuloma

KEY FACTS

TERMINOLOGY

- Synonym: Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE)
- Chronic traumatic ulceration of oral mucosa with unique histopathologic features

ETIOLOGY/PATHOGENESIS

- Accidental trauma from biting or fractured teeth
- Riga-Fede disease
 - Occurs in infants with natal or neonatal teeth
 - Ulceration of ventral tongue caused by tongue thrusting
- Electrical and thermal injury
- Factitial injury

CLINICAL ISSUES

- Can occur anywhere in oral cavity
- Painful ulcer from 1 mm to > 1 cm
- Usually see zone of hyperkeratosis surrounding ulcer
- Induration mimicking squamous cell carcinoma

MICROSCOPIC

- Ulcer bed composed of granulation tissue with mixed chronic inflammatory cell infiltrate of lymphocytes, histiocytes, neutrophils, and occasionally plasma cells
- Pseudoepitheliomatous hyperplasia of adjacent epithelium can be seen
- Inflammation including scattered eosinophils extends into underlying muscle
- In subset of traumatic ulcers, atypical CD30(+) histiocytic cells are noted
 - Significance of these findings is uncertain
- Necrosis is a feature of traumatic ulcerations caused by thermal or electrical injury

TOP DIFFERENTIAL DIAGNOSES

- Recurrent aphthous stomatitis
- Cutaneous CD30(+) T-cell lymphoma
 - Considered only in subset of cases with atypical histiocytes

Traumatic Ulcerative Granuloma With Rim of Keratosis

(Left) TUGSE typically presents as an indurated ulcer with a keratotic rim as shown here on the lateral border of the tongue. Due to the nonhealing nature, squamous cell carcinoma is often clinically suspected. (Right) Pseudoepitheliomatous hyperplasia can be associated with TUGSE. Careful examination of the epithelium will not show any atypical features including mitotic activity or abnormal maturation. Clinically, TUGSE can mimic cancer, and the surgeon may submit the specimen to rule out cancer.

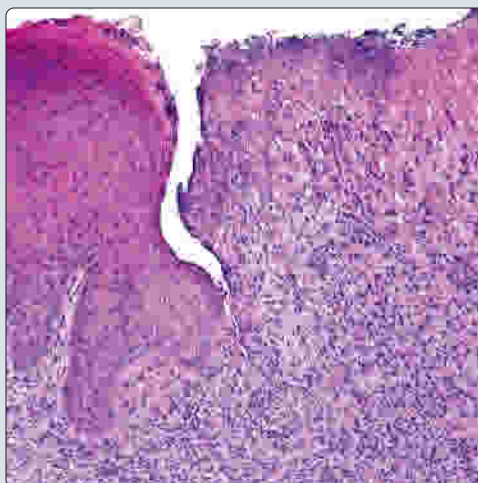


Pseudoepitheliomatous Hyperplasia

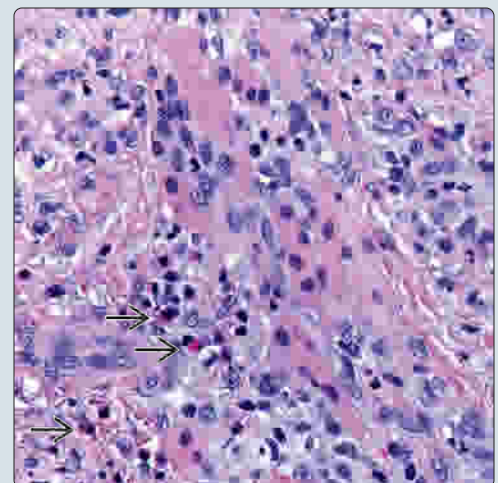


Traumatic Ulcerative Granuloma

(Left) Higher power photomicrograph shows the thickened fibrinopurulent covering and granulation tissue composed of a mixed inflammatory cell infiltrate. (Right) High-power photomicrograph demonstrates the mixed inflammatory cell infiltrate. Numerous eosinophils (boxed) are noted scattered throughout the striated muscle. Aphthous ulcers do not extend to the muscle, nor do they contain an eosinophilic cell infiltrate.



Eosinophils Usually Identified in Muscle



TERMINOLOGY

Synonyms

- Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE)
- Riga-Fede disease

Definitions

- Chronic traumatic ulceration of oral mucosa with unique histopathologic features

ETIOLOGY/PATHOGENESIS

Mechanical Damage

- Accidental trauma from biting
- Fractured or malposed teeth
- Sharp foodstuffs

Self-Inflicted Wound

- Parafunctional habits
 - Nocturnal clenching
 - Tongue and lip biting
- Riga-Fede disease
 - Occurs in infants with natal or neonatal teeth
 - Ulceration of ventral tongue caused by tongue thrusting
- Electrical and thermal injury
 - Electrical cords
 - Hot foods and beverages
- Factitial injury
 - Lesch-Nyhan syndrome
 - Tourette syndrome
 - Obsessive compulsive disorder

CLINICAL ISSUES

Epidemiology

- Incidence
 - True incidence unknown as is under reported
 - Less common than recurrent aphthous stomatitis
- Age
 - Newborns and infants
 - Riga-Fede disease
 - Children
 - Thermal and electrical burns
 - Parafunctional habits
 - Adults
 - Fractured &/or malposed teeth
 - Parafunctional habits
- Sex
 - Male > female

Site

- Can occur anywhere in oral cavity
- Lateral borders of tongue most common

Presentation

- Painful ulcer from 1 mm to > 1 cm
- Ulcer covered by fibrinopurulent membrane
- Usually see zone of hyperkeratosis surrounding ulcer
- Induration mimicking squamous cell carcinoma

Treatment

- Surgical approaches
 - Ulcers that do not resolve may need total excision
 - Biopsy of ulcer can initiate complete resolution
- Adjuvant therapy
 - Intralesional steroid injections

Prognosis

- Recurrence is common
- Source of trauma must be removed if possible

MICROSCOPIC

Histologic Features

- Ulcer covered by thickened fibrinopurulent membrane
- Pseudoepitheliomatous hyperplasia of adjacent epithelium can be seen
- Ulcer bed composed of granulation tissue with mixed chronic inflammatory cell infiltrate lymphocytes, histiocytes, neutrophils, and occasionally plasma cells
- Inflammation including scattered eosinophils extends into underlying muscle
- In subset of traumatic ulcers, atypical histiocytic cells are noted
 - Cells are pleomorphic and mitotic figures can be seen
 - Cells are CD30(+) and monoclonal rearrangement has been reported
 - Lymphocytes and eosinophils are admixed with atypical cells
 - Significance of these findings is uncertain
- Necrosis is a feature of traumatic ulcerations caused by thermal or electrical injury

DIFFERENTIAL DIAGNOSIS

Recurrent Aphthous Stomatitis

- Ulcer superficial and does not extend to muscle

Cutaneous CD30(+) T-Cell Lymphoma

- Considered only in subset of cases with atypical histiocytes

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KEY FACTS

ETIOLOGY/PATHOGENESIS

- Cheek, tongue, or lip biting
- Toothbrush abrasion: Mostly seen on gingiva
- Ill-fitting dentures or malposed teeth

CLINICAL ISSUES

- **Presentation**
 - Most common presentation is **linea alba**: Single white line on buccal mucosa approximating occlusal (bite) plane
 - Thickened white areas of cheeks, tongue, or lips
 - Surface can have irregular or shredded appearance
 - Occasionally may see erythema or petechiae
- **Prognosis**
 - Reactive lesion with no malignant potential

MICROSCOPIC

- Acanthotic stratified squamous epithelium with marked para/orthokeratosis

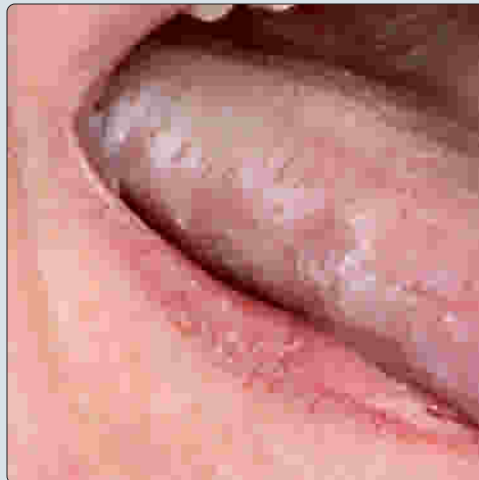
- Keratin surface may be smooth
- Shaggy keratin associated with biting habit
- Bacterial colonies often seen on surface
- No atypia should be seen
- Variable amounts of chronic inflammation in superficial lamina propria

TOP DIFFERENTIAL DIAGNOSES

- **Oral hairy leukoplakia**
 - HIV-associated disease **positive** for EBER
- **Smokeless tobacco keratosis**
 - Vestibule is most frequent location
- **Cinnamon stomatitis**
 - Increased number of inflammatory cells, including eosinophils with exocytosis
- **Oral leukoplakia**
 - Clinical term for lesions that cannot be attributed to other diseases
 - Can include dysplasia

Tongue Biting Habit

(Left) Frictional hyperkeratosis of right lateral tongue is seen in a patient with a chronic tongue-biting habit. (Right) Frictional hyperkeratosis of the buccal mucosa from cheek biting is usually seen along occlusal plane. This is termed linea alba when only a single, well-defined area of keratosis is seen along the occlusal plane. At times, lower labial mucosa is also involved and can be contiguous with buccal mucosa. Other common sites of frictional keratosis include attached gingiva from toothbrush abrasion and edentulous alveolus.



Frictional Keratosis Due to Cheek Biting



Chronic Lip Biting

(Left) Both the upper and lower lip can exhibit frictional keratosis. Patients can develop parafunctional habits whereby the lips are constantly rubbed against the teeth, resulting in hyperkeratosis. Most patients are unaware of this habit. (Right) High-power view of oral frictional keratosis shows a prominent granular cell layer. The superficial keratin has a shredded appearance consistent with tongue biting. Often bacteria colonies are noted on the surface keratin. Inflammation may or may not be present.



Shredded Keratin With Bacteria



KEY FACTS

TERMINOLOGY

- Reactive epithelial hyperplasia with extension of rete into deep lamina propria mimicking invasive squamous cell carcinoma
- Abbreviations: Pseudoepitheliomatous hyperplasia (PEH)

ETIOLOGY/PATHOGENESIS

- **Lesions associated with PEH**
 - Granular cell tumor (GCT)
 - Hyperplastic candidiasis
 - Inflammatory papillary hyperplasia
 - Median rhomboid glossitis
 - Mucosal ulcers
 - Necrotizing sialometaplasia

MICROSCOPIC

- Marked epithelial hyperplasia
- Rete can extend deeply into lamina propria
 - Anastomoses of tongue-like projections

- Keratin pearl formation can occur
- No or very little cytologic atypia
- Mitotic figures may be present but never atypical
- Neutrophilic microabscesses in keratin may be seen in candidiasis-associated PEH
- Infectious and ulcerative PEH will have inflammation

TOP DIFFERENTIAL DIAGNOSES

- **Well-differentiated squamous cell carcinoma**
 - Cytologic atypia is generally present
 - Nuclear pleomorphism and mitoses
- **GCT** often occurs on dorsal tongue, rare site for oral cancer
- **Candidiasis:** Cellular atypia in PEH should be reevaluated clinically after antifungal treatment
- **Necrotizing sialometaplasia**
 - Superficial biopsies may only demonstrate metaplastic ducts of minor salivary glands
 - No cytologic atypia

Pseudoepitheliomatous Hyperplasia of Palate



Pseudoepitheliomatous Hyperplasia Associated With Candidiasis

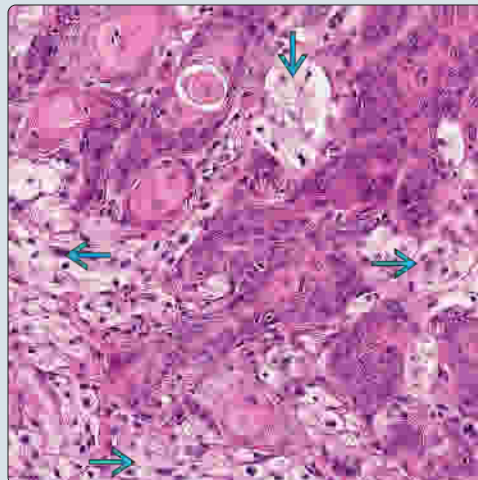


(Left) Biopsy of the hard palate in a patient with ill-fitting dentures shows inflammatory hyperplasia exhibiting PEH. Often this condition shows candidal hyphae and spores in the superficial keratin. (Right) Prominent PEH from a biopsy of the tongue associated with candidiasis is shown. Note the neutrophilic microabscess in the superficial keratin. PAS staining highlighted the presence of hyphae and spores. Squamous pearl formation is present but no cytologic atypia.

Metaplastic Ducts in Necrotizing Sialometaplasia



Granular Cell Tumor With Pseudoepitheliomatous Hyperplasia



(Left) Superficial biopsy of a nonhealing ulcer on the hard palate shows necrotizing sialometaplasia. The metaplastic ducts can be mistaken for a superficial squamous cell carcinoma. This entity usually occurs on the hard palate, an unusual location for oral cancer. (Right) Granular cell tumor with florid PEH is shown. Despite marked individual cell keratinization, no mitoses or cytologic atypia is present. Tongue-like projections show anastomoses, mimicking carcinoma.

Necrotizing Sialometaplasia

KEY FACTS

TERMINOLOGY

- Reactive inflammatory condition of salivary glands leading to coagulative necrosis of salivary acini and squamous metaplasia of ductal structures

CLINICAL ISSUES

- Majority of lesions affect minor salivary glands, especially of hard palate or junction of hard and soft palates
- Swelling eventually replaced by crater-like ulcer
- May be associated with numbness or pain
- No treatment required after diagnosis, as lesions are self-healing

MACROSCOPIC

- Crater-like ulcer
- Usually 1-5 cm

MICROSCOPIC

- Histologic picture is of acinar coagulative necrosis and squamous metaplasia of salivary gland ducts

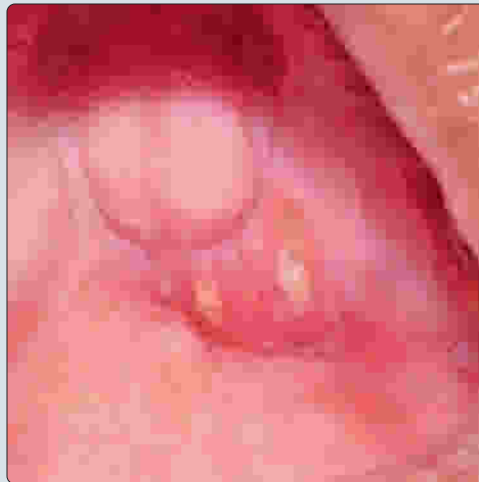
- Despite necrosis, **lobular architecture** of gland is maintained
- Variably dense subacute inflammatory infiltrate will be present in surrounding tissues &/or encompassing mucin pools
- Pseudoepitheliomatous hyperplasia of overlying squamous mucosal epithelium may be evident
 - May simulate malignancy

TOP DIFFERENTIAL DIAGNOSES

- Squamous cell carcinoma (SCC)**
 - PEH and nests of squamous epithelium in connective tissues may mimic SCC
 - Especially important when poorly oriented or inadequate biopsy
- Mucoepidermoid carcinoma (MEC)**
 - Mucin pools and squamous epithelium may mimic MEC
 - MEC tends to show epidermoid cells rather than true squamous cells

Palate Ulcer of Necrotizing Sialometaplasia

(Left) Multiple crater-like ulcerations present at the junction of the hard and soft palate just posterior to a maxillary tori are shown. The lesion initially presents as a nonulcerated swelling, but after a few weeks the necrotic tissue sloughs off, leaving ulcer(s). (Right) H&E shows an early lesion of necrotizing sialometaplasia associated with residual fibrous bands [B], which preserve the lobular architecture. Acinar coagulative necrosis and squamous epithelial nests are seen.

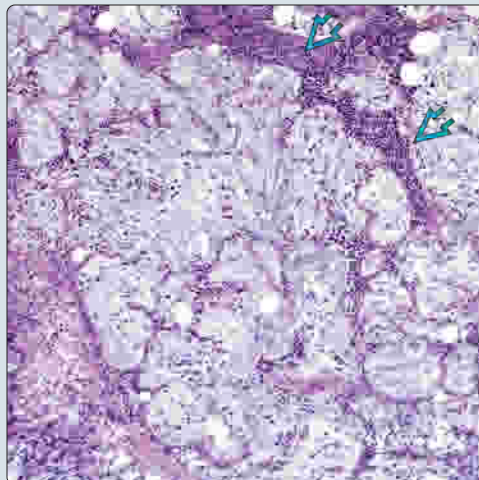


Maintained Lobular Architecture With Necrosis

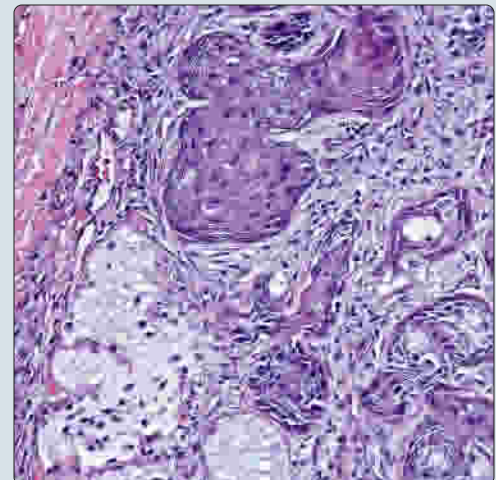


Necrotic Acini Maintain Lobular Architecture

(Left) Necrotizing sialometaplasia shows multiple necrotic mucinous acini with loss of nuclei and cell borders, yet maintenance of the overall acinar architectural pattern. Mucin extravasation is eliciting an inflammatory response [B]. (Right) In this medium-power view of necrotizing sialometaplasia, you can see the necrotic minor salivary gland mucinous acini in the bottom left, and ductal squamous metaplasia in the top center. The squamous proliferation has a bland cytologic appearance.



Ductal Squamous Metaplasia



TERMINOLOGY

Abbreviations

- Necrotizing sialometaplasia (NSM)

Definitions

- Reactive, self-healing inflammatory condition of salivary glands leading to coagulative necrosis of salivary acini and squamous metaplasia of ductal structures

ETIOLOGY/PATHOGENESIS

Reactive/Inflammatory Condition

- Etiology is speculative
- Likely due to vascular compromise leading to ischemic necrosis
 - Commonly associated with trauma due to dental treatment, surgery, or other iatrogenic events
 - Ill-fitting dentures, upper respiratory tract infections, and adjacent neoplasms or cysts have also been implicated
 - Often patient cannot recall inciting event

CLINICAL ISSUES

Epidemiology

- Age
 - Mean: 5th decade
 - Wide range: 1st to 9th decades
- Sex
 - Male > female

Site

- Majority of lesions affect minor salivary glands of oral cavity
 - Hard & soft palate most commonly affected (~ 75%)
 - Typically unilateral
 - Occasional bilateral or midline presentation
 - Lower lip, tongue, retromolar pad, and buccal mucosa occasionally affected
 - Upper aerodigestive tract sites may uncommonly be affected
 - Sinonasal tract and larynx
- < 10% of lesions involve major salivary glands

Presentation

- Initially presents as swelling of affected area
 - Swelling eventually replaced by crater-like ulcer
 - Rarely affects underlying palatal bone
 - May be associated with numbness or pain

Treatment

- No treatment required after diagnosis, as lesions are self-healing
 - Slowly heals in 3-12 weeks (average: 5-6 weeks)
 - Surgical debridement and sterile saline rinses may assist in healing

MACROSCOPIC

General Features

- Crater-like ulcer

Size

- Usually 1-5 cm

MICROSCOPIC

Histologic Features

- Acinar coagulative necrosis and squamous metaplasia of salivary gland ducts
- Despite necrosis, **lobular architecture** of gland is maintained
 - General outlines of necrotic salivary acini are present
- Squamous metaplasia of ductal structures presents as smooth, rounded nests of squamous epithelium
 - Residual ductal lumina and possible mucocytes may be present
 - Dysplastic changes, such as pleomorphism, nuclear hyperchromasia, and abnormal mitotic figures, are rare to absent
- Variably dense, subacute inflammatory infiltrate may be present in surrounding tissues &/or encompassing mucin pools
- Pseudoepitheliomatous hyperplasia (PEH) of overlying squamous mucosal epithelium may be evident
 - PEH sometimes appears to merge with ductal squamous metaplasia, suggesting malignancy

DIFFERENTIAL DIAGNOSIS

Squamous Cell Carcinoma (SCC)

- PEH and nests of squamous epithelium in connective tissues may mimic SCC
 - Especially important when poorly oriented or inadequate biopsy
- Features favoring NSM vs. SCC
 - Maintained lobular salivary gland architecture
 - Presence of acinar coagulative necrosis
 - Round to ovoid nests of metaplastic squamous cells with smooth borders, lacking cytologic atypia

Mucoepidermoid Carcinoma (MEC)

- Mucin pools and squamous epithelium may suggest MEC
- Features of NSM that may help distinguish from MEC
 - Maintained lobular salivary gland architecture
 - No invasion and minimal cyst formation
 - No intermediate or clear cell proliferations
 - Formation of true squamous islands
 - MEC tends to show epidermoid cells rather than true squamous cells

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KEY FACTS

TERMINOLOGY

- Lymphangiomatous polyp (LAP): Lymphangioma arising from palatine tonsil

CLINICAL ISSUES

- Mean age: 25 years; range: 3-50 years
- Obstructive symptoms (size dependent)
- Dysphagia &/or sore throat
- Sensation of mass in throat (globus)

MACROSCOPIC

- Unilateral, polyp
- Mean: 1.6 cm; can reach up to 8 cm

MICROSCOPIC

- Polypoid or papillary projections
- Prominent, dilated vascular channels
- Fibrous connective tissue and lymphoid elements
- Intact surface with hyperplasia

ANCILLARY TESTS

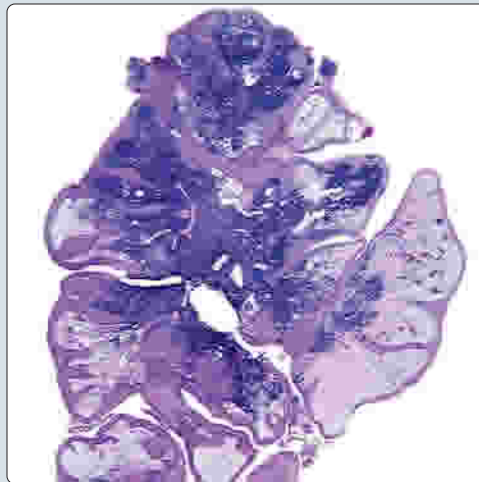
- Endothelium **positive**: CD31, CD34, FVIIIIRAg, VEGF-1, podoplanin (D2-40)

TOP DIFFERENTIAL DIAGNOSES

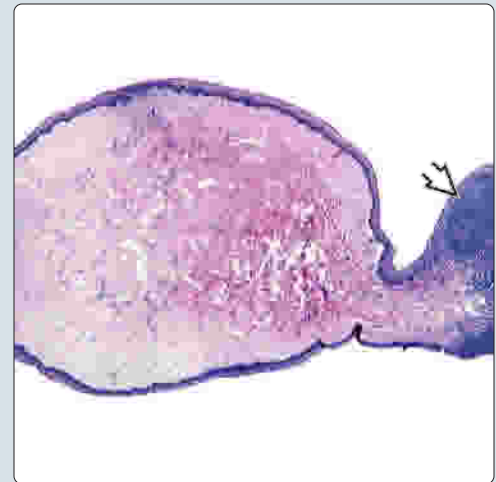
- Juvenile angiofibroma (nasopharyngeal)
 - Males exclusively; nasopharynx, destructive large lesion, epistaxis, cellular stroma, variable vascular channels
- Papillary lymphoid polyp
 - Exclusively in children; papillary, prominent lymphoid follicles (development arc with LAP)
- Hemangioma
 - Dilated vessels with blood, no background stroma, lacks lymphocytes, tends to lack fibrosis
- Fibroma
 - No vascular component with heavily collagenized stroma
- Squamous papilloma
 - Multiple exophytic projections covered with layers of squamous epithelium, no lymphoid stroma

Papillary Architecture in Lymphangiomatous Polyp (LAP)

(Left) A low-power view demonstrates a polypoid structure with intact surface squamous epithelium. There are numerous vessels in the stroma, many associated with lymphocytes. The presence of lymphoid tissue and vascular proliferation distinguishes this from a squamous papilloma. (Right) A pedunculated structure is noted protruding from the tonsil [B], a common finding in a LAP. There is ample fibrosis associated with dilated vessels.

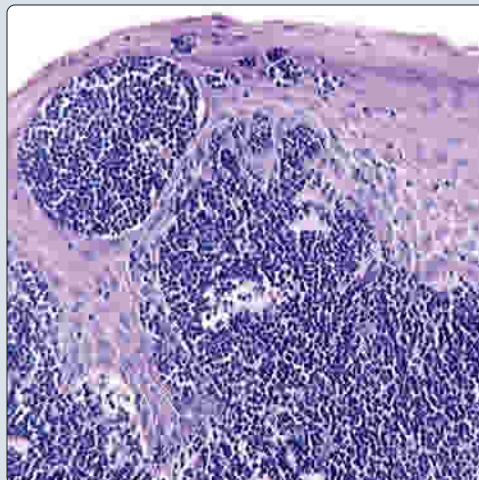


Polypoid LAP



Epitheliotropism of Lymphocytes

(Left) The lymphocytes may display epitheliotropism, aggregating in the epithelium in groups and clusters. The lymphocytes lack cytologic atypia. (Right) A proliferation of lymphovascular channels containing proteinaceous fluid [B] is shown. Lymphatic channels can be obscured by lymphocytes filling the channels but can be highlighted by endothelial markers, such as D2-40 and CD34. Adipocytes [B], as well as muscle, may be seen in the stroma.



Dilated Lymphovascular Channels



TERMINOLOGY

Abbreviations

- Lymphangiomatous polyp (LAP)

Synonyms

- Lymphangiectatic fibrous polyp
- Fibrovascular polyp
- Polypoid lymphangioma
- Papillary lymphoid polyp
- Lymphoid papillary hyperplasia
- Angioma
- Angiofibroma
- Fibroangioma
- Fibrolipoma

Definitions

- Lymphangioma arising from palatine tonsil

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Stroma is more abundant than vessels
- Probably hamartoma rather than neoplasm
 - Haphazard proliferation of elements normally present in tonsil

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare (~ 2% of all tonsillar tumors)
 - > 90% of lymphangiomatous polyps develop in skin and subcutaneous tissues of head and neck
- Age
 - Mean: 25 years
 - Range: 3-50 years
- Sex
 - Equal gender distribution

Site

- Palatine tonsil

Presentation

- Dysphagia
- Sore throat
- Sensation of mass in throat (globus)
- Obstructive symptoms (size dependent)
- Lesions are frequently present for years

Treatment

- Surgical approaches
 - Simple excision

Prognosis

- Mass may cause ball-valve effect if not removed

MACROSCOPIC

General Features

- Unilateral polyp

Size

- Mean: 1.6 cm

- Range: Up to 8 cm

MICROSCOPIC

Histologic Features

- Polypoid or papillary projections
- Prominent, dilated vascular channels
 - Usually not as prominent as typical lymphangioma
- Intact surface with hyperplasia
 - Lymphocytic epitheliotropism focally
- Vascular proteinaceous fluid with lymphocytes
- Variable stroma
 - Stroma consists of fibrous connective tissue and lymphoid elements
 - Fat and muscle may be present
 - Tends to be paucicellular fibrous background stroma

ANCILLARY TESTS

Immunohistochemistry

- Endothelium **positive**: CD31, CD34, FVIIIIRAg, VEGF-1, podoplanin (D2-40)
- Polytypic lymphoid cells; although, T cells (CD3) predominate

DIFFERENTIAL DIAGNOSIS

Juvenile Angiofibroma (Nasopharyngeal)

- Males exclusively; nasopharynx, destructive large lesion, epistaxis, cellular stroma, variable vascular channels

Papillary Lymphoid Polyp

- Exclusively in children; papillary, prominent lymphoid follicles (development arc with LAP)

Hemangioma

- Dilated vessels with blood, no background stroma, lacks lymphocytes, tends to lack fibrosis

Fibroma

- No vascular component with heavily collagenized stroma

Squamous Papilloma

- Multiple exophytic projections covered with layers of squamous epithelium, koilocytic atypia, no lymphoid stroma, no vascular proliferation

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KEY FACTS

TERMINOLOGY

- Snuff dipper's keratosis: Hyperkeratosis of mucosa associated with smokeless tobacco contact
- Nicotine stomatitis: Mucosal change of palate associated with heat of smoking
- Smoker's melanosis: Increased oral pigmentation associated with smoking

CLINICAL ISSUES

- Snuff dipper's keratosis: Soft, fissured, gray-white lesion in area where tobacco is usually held in mouth
- Nicotine stomatitis: Numerous red papules of palate
- Smoker's melanosis: Diffuse melanin pigmentation, affects any mucosal surface but most commonly anterior facial gingiva

MICROSCOPIC

- **Snuff dipper's keratosis**
 - Surface epithelium thickened with chevron appearance

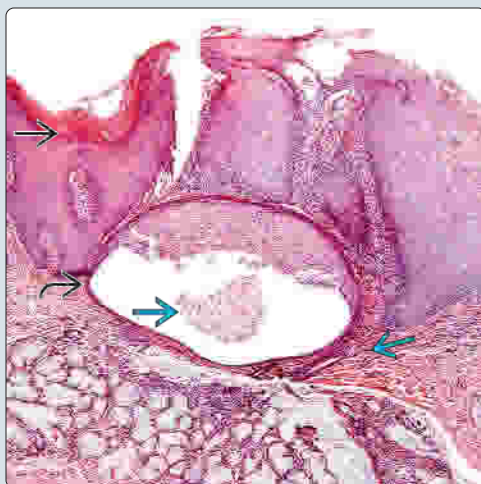
- Acanthosis
- Dysplasia is not featured
- **Nicotine stomatitis**
 - Chronic inflammation of connective tissue and minor salivary glands
 - Squamous metaplasia of excretory ducts, inflammation may be seen within lumen
- **Smoker's melanosis**
 - Increased melanin pigmentation associated with basal cell layer of epithelium
 - Melanin incontinence seen in superficial lamina propria

TOP DIFFERENTIAL DIAGNOSES

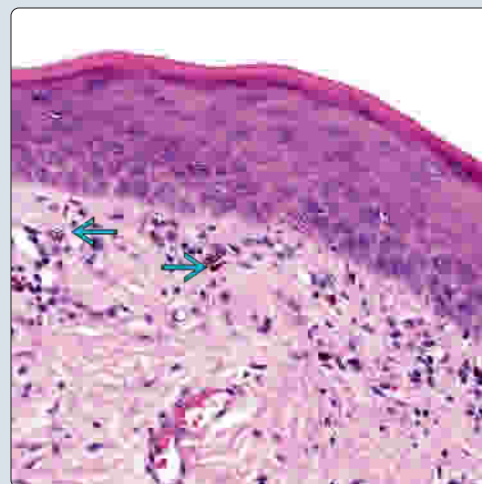
- Must exclude malignancy
 - Squamous cell carcinoma should be considered in nicotine stomatitis and snuff dipper's keratosis
 - Melanoma must be excluded for smoker's melanosis

Histology of Nicotine Stomatitis

(Left) Intermediate-power image shows hyperkeratosis of the overlying acanthotic epithelium. Squamous metaplasia of the excretory gland with surrounding inflammatory infiltrate are other associated findings. (Right) There is a subtle increased melanin pigmentation along the basal membrane with melanin incontinence in the superficial lamina propria. The histologic findings are identical to racial pigmentation or melanotic macule, requiring a patient smoking history for diagnosis.

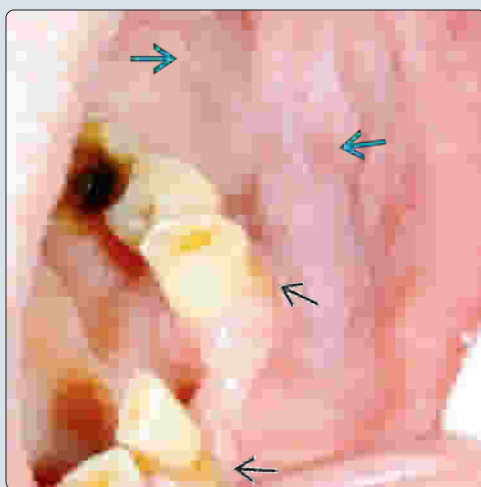


Histology of Smoker's Melanosis

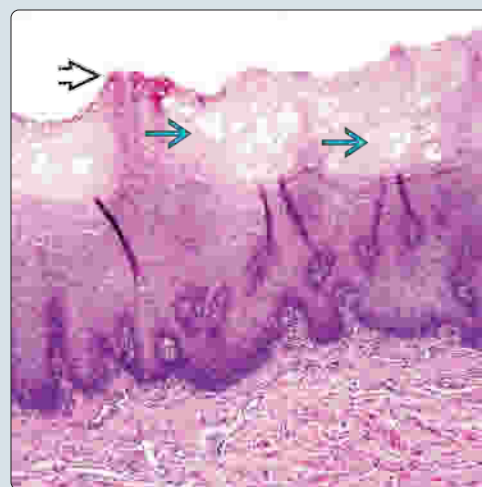


Clinical Image of Snuff Dipper's Keratosis

(Left) Clinical photo shows white, fissured areas in the mandibular vestibule; the location this patient places and holds his chewing tobacco. Gingival recession is often seen in conjunction with these lesions. After tobacco cessation, there is slow resolution. (Right) Snuff dipper's keratosis demonstrates hyperkeratinized and acanthotic epithelium. Parakeratin chevrons are a classic histologic finding. Cells within the epithelium may show intracellular vacuolization.



Histology of Snuff Dipper's Keratosis



TERMINOLOGY

Synonyms

- **Snuff dipper's keratosis:** Spit tobacco keratosis, tobacco pouch keratosis
- **Nicotine stomatitis:** Smoker's palate

Definitions

- Oral changes associated with habitual use of tobacco products
 - Snuff dipper's keratosis: Hyperkeratosis of the mucosa associated with smokeless tobacco contact
 - Nicotine stomatitis: Mucosal change of palate associated with heat of smoking
 - Smoker's melanosis: Increased oral pigmentation associated with smoking

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Tobacco
- Heat is associated with nicotine stomatitis
 - Higher association with reverse smoking (smoking with lit end of cigarette in mouth and pipe smoking)

CLINICAL ISSUES

Epidemiology

- Snuff dipper's keratosis is common, occurring in up to 60% of smokeless tobacco users
- Nicotine stomatitis and smoker's melanosis is relatively rare
 - Smoker's melanosis is more common in women; thought to be result of interactions of hormones

Presentation

- Snuff dipper's keratosis: Soft, fissured, gray-white lesion in area where tobacco is usually held in mouth
 - Maybe associated with gingival recession, increased caries, and staining of teeth
- Nicotine stomatitis: Numerous red papules of palate
 - Tissue may have gray or white appearance, keratinization becoming so thick it creates dried mud appearance
 - May be associated with whiteness of gingiva and buccal mucosa
- Smoker's melanosis: Diffuse melanin pigmentation, affects any mucosal surface but most commonly anterior facial gingiva

Treatment

- Cessation of tobacco use

Prognosis

- Lesions should resolve slowly without further contact with heat or tobacco
- While none of the lesions are considered premalignant, tobacco use is risk factor for oral carcinoma

MICROSCOPIC

Histologic Features

- Snuff dipper's keratosis
 - Nonspecific
 - Epithelium acanthotic

- Parakeratin chevrons may be seen within thickened superficial epithelium
- Dysplasia is not featured
- Nicotine stomatitis
 - Hyperkeratosis and acanthosis
 - Chronic inflammation of connective tissue and minor salivary glands
 - Squamous metaplasia of excretory ducts, inflammation may be seen with in lumen
- Smoker's melanosis
 - Increased melanin pigmentation associated with basal cell layer of epithelium
 - Melanin incontinence seen in superficial lamina propria

DIFFERENTIAL DIAGNOSIS

Squamous Cell Carcinoma

- Especially verrucous squamous cell carcinoma with broad pushing border and marked church spire hyperkeratosis and parakeratotic crypting compared to snuff dipper's keratosis
- Compared with nicotine stomatitis, there is pleomorphism, disorganization, increased mitoses, atypical mitoses, and invasive growth

Frictional Hyperkeratosis

- Acantholytic stratified squamous epithelium with marked para- and orthokeratosis
- Shaggy or shredded keratin with bacterial colonies on surface
- No atypia with only limited inflammation

Atrophic Candidiasis

- Epithelial hyperplasia with parakeratin, inflammatory exocytosis, and fungal organisms at surface

Pigmentation (for Smoker's Melanosis)

- Exogenous pigmentation: Foreign body tattoo, drug-related discoloration
- Endogenous pigmentation: Racial pigmentation, melanotic macule, nevus, blue nevus, melanoacanthoma, melanoma

Inflammatory Papillary Hyperplasia (for Nicotine Stomatitis)

- Papillary projections of squamous epithelium with rich inflammatory investment

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- History of tobacco use is essential for diagnosis

SELECTED REFERENCES

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Amalgam Tattoo

KEY FACTS

TERMINOLOGY

- Localized area of blue, gray, or black pigmentation caused by amalgam embedded into oral tissues, usually during dental procedures

ETIOLOGY/PATHOGENESIS

- Commonly used dental amalgam, which contains silver, tin, mercury, and other materials, can be embedded into tissue during dental procedures

CLINICAL ISSUES

- Presentation**
 - Blue-gray to black pigment most common on gingiva and buccal mucosa
 - Asymptomatic flat macule ranging from a few mm to > 1 cm
- Treatment**
 - Biopsy indicated if clinical diagnosis is uncertain
 - Can be removed for cosmesis

IMAGING

- Generally not visible radiographically

MICROSCOPIC

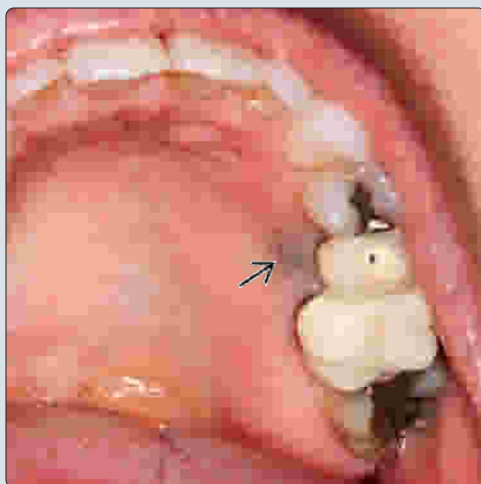
- Fine black granules within superficial connective tissue
- Pigment can be seen in collagen, histocytes, fibroblasts, elastic fibers, and around blood vessel walls
- Usually no inflammation associated with pigment
- Up to 38% of cases have foreign giant cell reaction

TOP DIFFERENTIAL DIAGNOSES

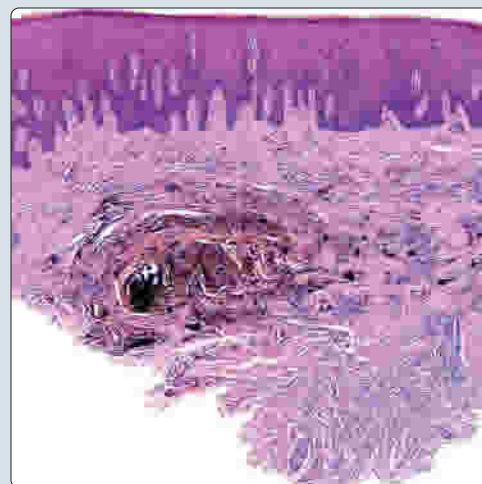
- Pigmented intraoral lesions**
 - Oral melanotic macule
 - Intraoral melanocytic nevus
 - Oral melanoma
- Varicosities**
- Unintentional mucosal tattoos**
 - Accidental placement of foreign material, such as pencil graphite

Clinical Photograph of Amalgam Tattoo

(Left) Clinical photo shows diffuse blue-gray pigmentation typical for an amalgam tattoo. The tattoo could be related to the crowns on the premolar and molar teeth, or the amalgam restoration on the premolar tooth. (Right) H&E shows amalgam tattoo of the buccal vestibule with scattered large fragments of black material distributed in the lamina propria. The overlying epithelium is normal. Inflammation is noted, although many amalgam tattoos show little or no inflammation.

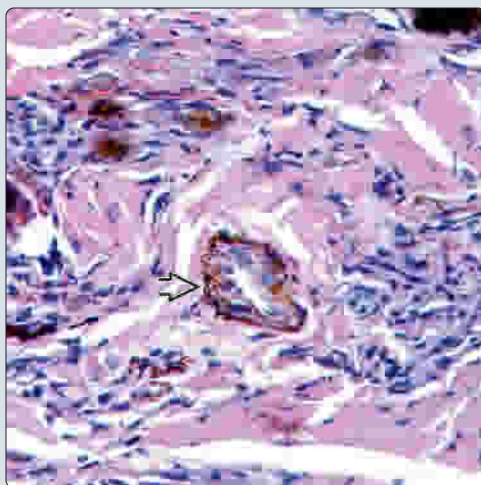


Dark Solid Clumps of Amalgam

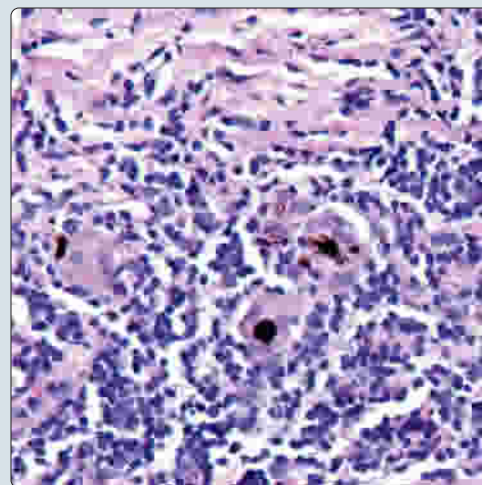


Amalgam Tattoo Encircling Vessel

(Left) High-power photomicrograph of an amalgam tattoo illustrates the perivascular location of the amalgam. The silver salts found in dental amalgam stain the reticulin fibers surrounding nerves and vessels. (Right) H&E shows amalgam tattoo eliciting a foreign body giant cell reaction. Amalgam pigment is seen within the scattered giant cells with associated plasma cells and lymphocytes. Radiographs can at times confirm the metallic nature of the tattoo.



Foreign Body Giant Cell Reaction



KEY FACTS

TERMINOLOGY

- **Definition**
 - Benign, ectopic sebaceous glands
- **Synonyms**
 - Ectopic sebaceous glands
 - Fordyce condition or spots

ETIOLOGY/PATHOGENESIS

- Considered normal variant
 - Thought to arise from ectoderm inclusions during fusion of mandible and maxilla

CLINICAL ISSUES

- More commonly noted in adults than in children
- Equal gender distribution
- ~ 60% of children < 10 years of age have Fordyce granules
- Most common on lateral margins of upper and lower lip and buccal mucosa
- Less frequent on gingiva, retromolar area, and soft palate

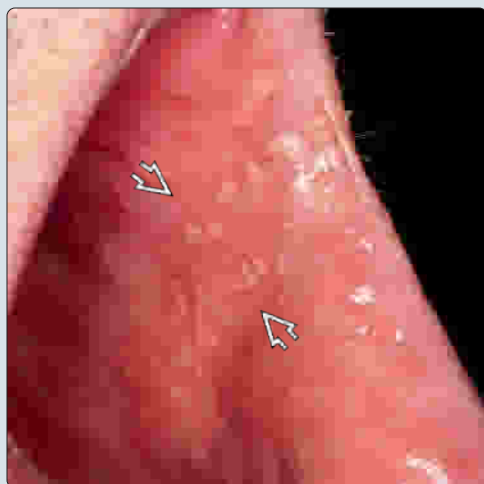
Presentation

- Incidental, asymptomatic
 - Multiple uniform-sized 1-3 mm yellow papules &/or plaques
 - Widely spaced or clustered to form plaques
- Normal variant and usually not treated

MICROSCOPIC

- Normal sebaceous glands lacking hair follicles
- Sebaceous hyperplasia can occur, particularly with advanced age
- May consist of only 1 lobule, but usually multiple acinar lobules are in superficial lamina propria
- Central duct extending to surface epithelium can be seen
- Each lobule is composed of peripheral layer of basophilic cuboidal cells
- Centrally located polygonal cells have abundant lipid-filled cytoplasm
- Glands can become obstructed, forming pseudocysts

Clinical Photo of Fordyce Granules



Acinar Lobules of Fordyce Granules



(Left) Fordyce granules present as asymptomatic, yellow papules on the buccal mucosa. They cannot be scraped off. (Right) The typical microscopic appearance of Fordyce granules is shown. Sebaceous glands are composed of acinar lobules beneath normal-appearing epithelium. Usually < 15 lobules are seen per gland, and > 15 lobules per gland is considered to be sebaceous hyperplasia.

Sebaceous Gland Duct Opens to Surface



Pseudocyst



(Left) High-power photomicrograph of Fordyce granules illustrates the central duct of the sebaceous lobule connecting the gland to the surface epithelium. (Right) Photomicrograph of a biopsy from the lip of Fordyce granules shows a pseudocyst; such a cyst generally develops in the excretory duct of the sebaceous gland. The cyst lumen generally contains keratin, sebum, &/or mucin. This is comparable to skin milia.

Hairy Tongue

KEY FACTS

TERMINOLOGY

- Black hairy tongue (BHT)
- Synonyms: Lingua villosa nigra
- Definition: Condition characterized by elongated filiform lingual papillae of tongue

ETIOLOGY/PATHOGENESIS

- Smoking
- Excessive consumption of tea or coffee
- Poor oral hygiene or oral hygiene products
- Substance abuse
- General debilitation
- Xerostomia
- Medications
- Radiation therapy to head and neck

CLINICAL ISSUES

- Prognosis: Excellent
- Presentation: Usually asymptomatic

- Elongated brown, yellow, or black matted papillae
- May present with cosmetic concerns
- Gagging or bad taste in mouth may be chief complaint
- Identification of offending cause and discontinuation if possible
- Reassurance and increased oral hygiene with debridement

MICROSCOPIC

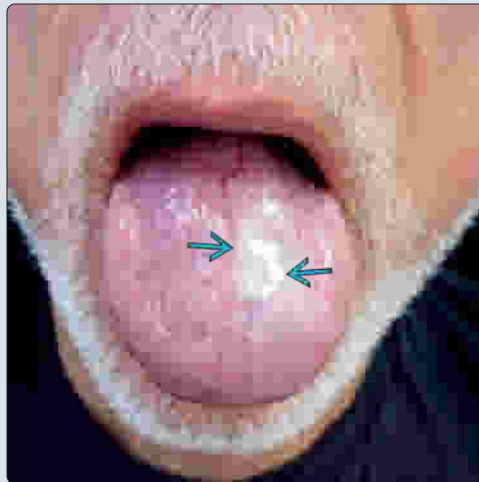
- Elongation and hyperkeratosis of filiform papillae
- Numerous colonies of surface bacteria
- Biopsy is rarely performed

TOP DIFFERENTIAL DIAGNOSES

- Frictional keratosis
- Hairy leukoplakia
- Candidiasis
- Leukoplakias
- Usually affects palate

Clinical Photo: Hairy Tongue

(Left) This image shows an older male with elongated filiform papillae of the midline tongue. The papillae can be white, yellow, brown or black. The clinical color is associated with the bacteria involved and other causative agents. Those affected with hairy tongue may complain about halitosis. (Right) Low-power image shows elongation and dense hyperkeratosis of the papillae of the epithelium.



Low-Power Image: Hairy Tongue

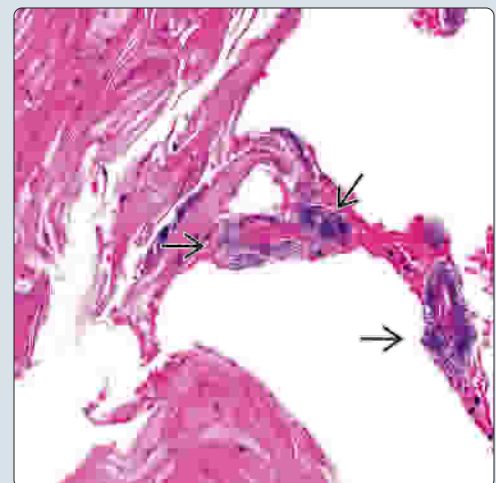


Medium-Power Image: Hairy Tongue

(Left) This image shows the keratinaceous debris associated with the underlying hyperkeratotic epithelium. It is easy to appreciate how this histologic image results in the clinical manifestation of the tongue appearing hairy. (Right) This high-power image shows the numerous bacterial colonies of the epithelial surface. Bacterial colonies are a nonspecific finding and are also seen in frictional keratosis and nonpathologic tissue samples of tongue.



High-Power Image: Hairy Tongue



KEY FACTS

TERMINOLOGY

- Normal structure located in buccotemporalis fascia bilaterally along medial surface of ascending ramus

ETIOLOGY/PATHOGENESIS

- Normal anatomical structure that persists throughout life

MICROSCOPIC

- Size ranges from 0.7-1.7 cm in length and 0.1-0.2 cm in width
- Circumscribed nests of benign-appearing squamous cells within fibrous stroma
 - Cells are uniform and bland in appearance
 - No mitotic figures are seen
 - Basement membrane noted around individual epithelial islands highlighted by PAS stain
- Keratinization is not seen
- Basaloid cells with nuclear palisading may be present
- Stroma rich in nerves

- Epithelial islands often intimately associated with nerves

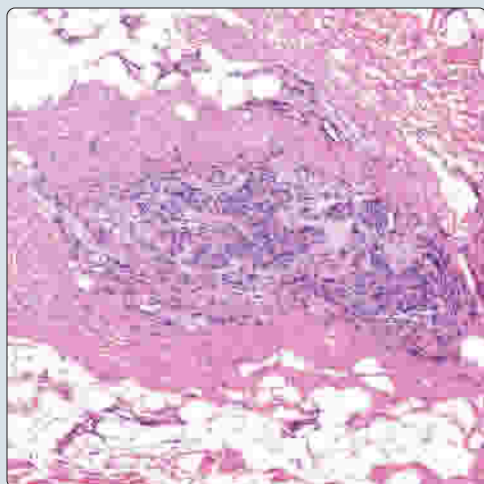
TOP DIFFERENTIAL DIAGNOSES

- Invasive neurotropic squamous cell carcinoma
 - Lack of basement membrane
 - Pleomorphism &/or mitotic figures
 - Keratinization or keratin pearls
- Mucoepidermoid carcinoma
 - Cystic, with mucocytes and epidermoid cells
- Adenoid cystic carcinoma
 - Strong perineural proclivity
 - Tends to have small, hyperchromatic nuclei

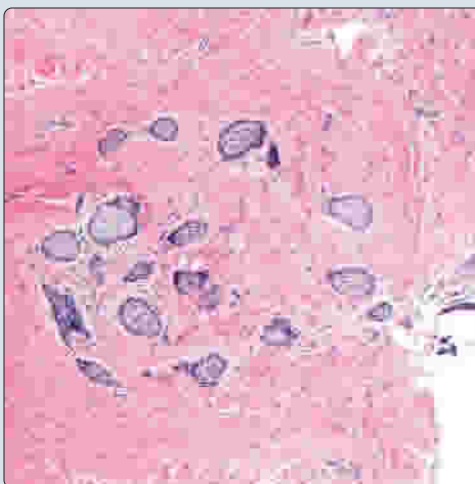
DIAGNOSTIC CHECKLIST

- **Pathologic interpretation pearls**
 - Communication with surgeon crucial to avoid misdiagnosing structures as invasive carcinoma
 - Juxtaoral organ of Chievitz can exhibit both intra- and perineural invasion

Juxtaoral Organ of Chievitz Embedded In Connective Tissue

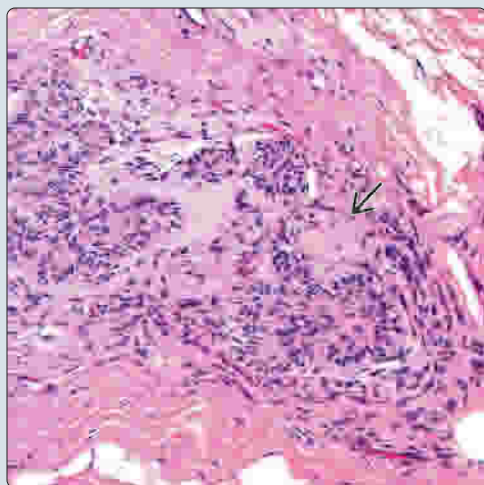


Juxtaoral Organ of Chievitz

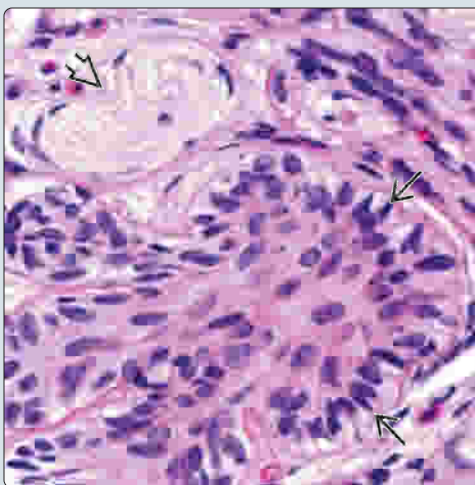


(Left) Described by Chievitz, a Danish histologist, the organ of Chievitz is located within the soft tissue overlying the angle of the mandible in the buccotemporal space. It is composed of nests of bland epithelium surrounded by connective tissue rich in nerves. (Right) The juxtaoral organ of Chievitz is between the fascia of the buccotemporal and pterygoid muscles and is innervated by the buccal nerve. The epithelial parenchyma form circumscribed cell nests without any cytologic atypia or keratinization.

Epithelial Cells Surrounding Small Nerve



Hyperchromatic Basal Cells With Palisading



(Left) Juxtaoral organ of Chievitz composed of nests of epithelial cells within a fibrofatty stroma is shown. These nests are intimately associated with small nerves (branches of the buccal nerve). This finding can be misinterpreted as perineural invasion. (Right) High-power view of the juxtaoral organ of Chievitz highlighting the hyperchromatic basal cells, some exhibiting nuclear palisading, is shown. This feature is not always noted. A small nerve twig is also seen.

Verruciform Xanthoma

KEY FACTS

TERMINOLOGY

- Benign inflammatory mucocutaneous lesion

CLINICAL ISSUES

- Most common in 5th-7th decades
- Slight male predominance (~ 60%)
- Gingiva and hard palate account for 75% of reported cases
- Extraoral sites include vulva, scrotum, penis, anal region, and extremities
- Usually well demarcated and slightly raised from surrounding mucosa
- Surface has papillary or granular appearance
- Recurrence rare

MICROSCOPIC

- Papillary epithelium with acanthosis
- Elongated narrow rete of uniform depth extend into lamina propria

- Parakeratin invaginates downward between epithelial projections
- Between elongated rete are collections of large xanthoma cells

ANCILLARY TESTS

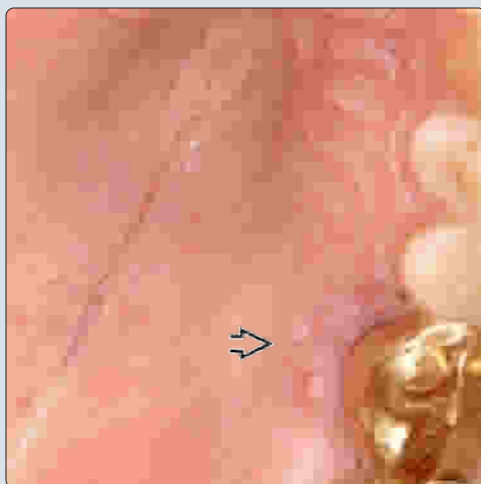
- Xanthoma cells are PAS(+), diastase resistant
- Cytoplasm of xanthoma cells are **positive** for lipid stains (Sudan III, Scharlach R)
- Xanthoma cells are CD68(+) and S100(-)

TOP DIFFERENTIAL DIAGNOSES

- Histology is distinct as xanthoma cells are hallmark of verruciform xanthoma (VX)
- Verrucous carcinoma
 - Rete are bulbous rather than the narrow rete seen in VX

Verruciform Xanthoma of Palate

(Left) Verruciform xanthoma (VX) presenting as a red and white lesion of the hard palate is shown. The lesion is slightly exophytic with a papillary surface. Clinically, this can be mistaken for a papilloma, granular cell tumor, or verrucous hyperplasia. The alveolar mucosa is the most common location for VX, accounting for 75% of reported cases. (Right) Low-power microscopic image of VX shows a papillary lesion with hyperparakeratosis. The rete ridges are elongated to a uniform depth.



Papillary Pattern of Verruciform Xanthoma



Parakeratin Plugging in Verruciform Xanthoma

(Left) Medium-power photomicrograph illustrates the parakeratin plugging typical in VX. The clefts between the epithelial projections are filled with parakeratin, which often have an orange coloration. (Right) The hallmark of VX is the collection of large macrophages with foamy cytoplasm located in the connective tissue papillae. These foam cells are positive for CD68 consistent with a macrophage lineage and are PAS(+), diastase resistant.



Xanthoma Cells



KEY FACTS

TERMINOLOGY

- Histologically normal salivary gland tissue located in unusual or abnormal anatomic location
- Synonyms
 - Salivary heterotopia, salivary gland choristoma, ectopic salivary glands

CLINICAL ISSUES

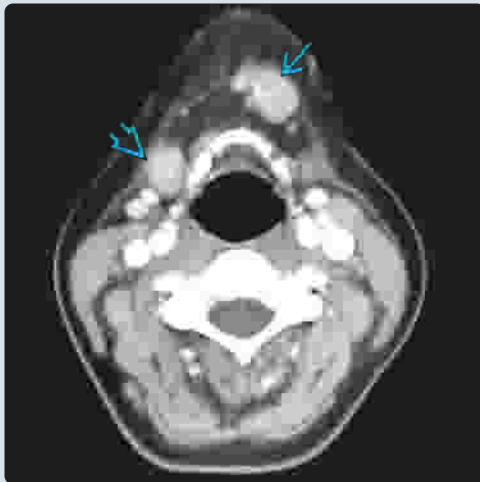
- Found incidentally
- Majority of heterotopic salivary glands located within structures of head and neck (H&N)
 - Middle ear, external ear
 - Neck, thymus, mandible (intraosseous)
 - Parathyroid gland, thyroid gland, cervical and periparotid lymph node
- Non-H&N sites may include mediastinum, stomach, prostate gland, rectum, vulva
- May be discovered due to signs and symptoms associated with inflammation or neoplasia

- Heterotopic salivary gland tissue in neck may present as draining sinus
 - Most common on right side
 - Frequently associated with lower anterior sternocleidomastoid muscle
- No treatment required if incidental finding

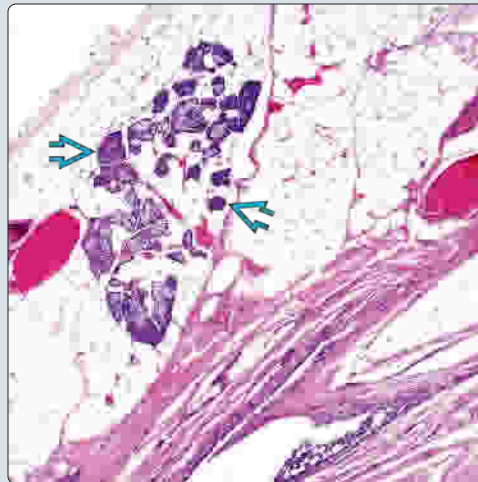
MICROSCOPIC

- Histologic presentation akin to normal minor salivary gland tissue
 - Salivary lobules separated by fibrous septa
- Glandular cell types
 - Pure mucous
 - Pure serous
 - Combination of glandular acini (mucoserous)
- Associated pathologic conditions will be in keeping with specific diagnosis
 - May include cyst formation, oncocytic metaplasia/hyperplasia, benign or malignant neoplasms

CT: Heterotopic Salivary Gland Tissue

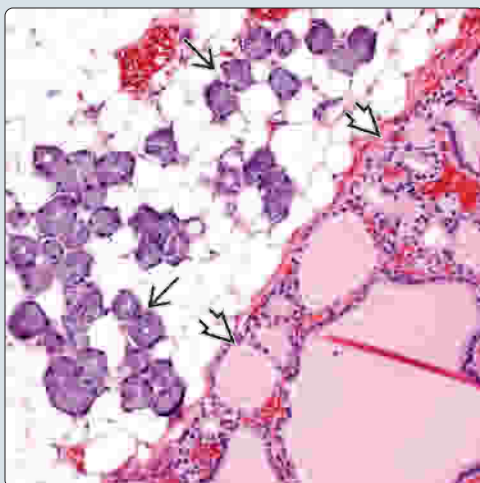


Heterotopic Salivary Gland in Neck



(Left) Axial CECT shows accessory salivary gland tissue [blue box] just to the left of the midline within the soft tissue. The density and enhancement is similar to the normal submandibular gland [blue box]. This patient was symptomatic. (Right) This specimen was removed from the lateral neck for an unrelated condition. While well away from major or minor salivary glands, this heterotopic salivary gland [blue box] shows histologic features of minor salivary glands.

Glands Adjacent to Thyroid Gland



Seromucous Glands From Middle Ear



(Left) The salivary gland parenchyma is normal in architecture and arrangement [blue box], but it is identified immediately adjacent to the thyroid gland [blue box]. This is considered ectopic or heterotopic tissue. (Right) H&E shows heterotopic minor salivary glands [blue box] displaying ductal ectasia and sialadenitis. Seromucous glands are typical in the cartilaginous/nasopharynx portion of the eustachian tube but are not typical near the middle ear (pictured).

Geographic Tongue

KEY FACTS

TERMINOLOGY

- Synonyms
 - Erythema migrans, benign migratory glossitis, psoriasiform mucositis
- Definition
 - Benign inflammatory condition, primarily of tongue with unknown etiology

CLINICAL ISSUES

- 1-2.5% of population
- Primarily tongue
- Usually asymptomatic
- Multiple, well-defined areas of erythema surrounded by raised white-yellow borders that appear rapidly
- Lesions appear to move or migrate around surface of tongue
- Healing occurs within days or weeks, then lesions develop in another area

MICROSCOPIC

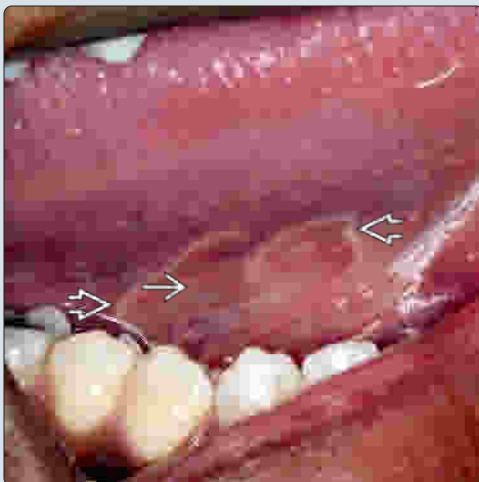
- Epithelium
 - Hyperparakeratosis
 - Acanthosis
 - Spongiosis
 - Elongated rete ridges
 - Munro microabscesses
- Lamina propria
 - Lymphocytic infiltration
 - Neutrophilic infiltration
- Reminiscent of psoriasis

TOP DIFFERENTIAL DIAGNOSES

- Candidiasis
- Lichen planus
- Lichenoid mucositis
- Psoriasis
- Contact stomatitis

Clinical Photo of Geographic Tongue

(Left) Clinical photograph of a geographic tongue shows well-demarcated erythematous areas surrounded by a yellow-white border. The ventral tongue location is a little unusual, however, lesions appear to migrate around the tongue and, less commonly, the oral cavity. (Courtesy K.M. Goodin, DDS.) (Right) Hematoxylin and eosin shows the characteristic low-power presentation of a geographic tongue with distinctive, elongated rete ridges and parakeratosis.

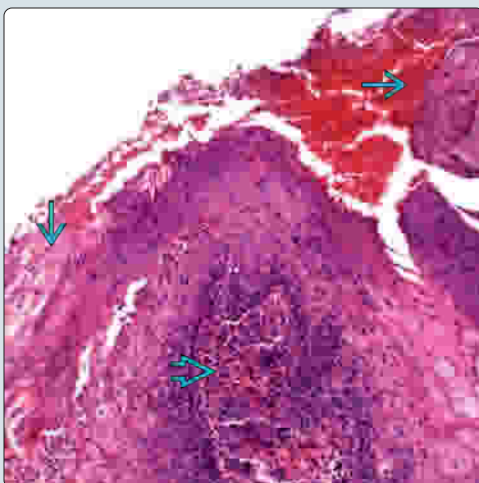


Elongated Rete Ridges

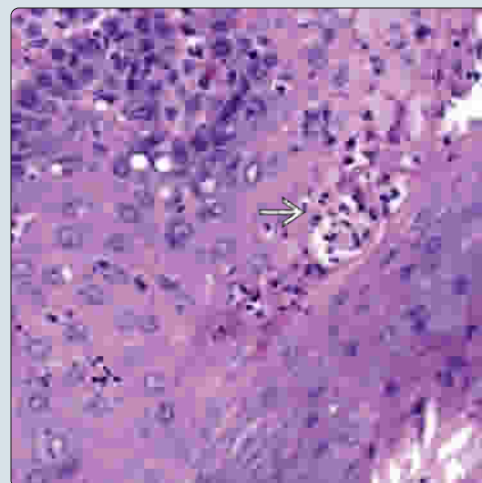


Hyper- and Parakeratosis of Epithelial Surface

(Left) A medium-power view of the inflamed epithelial surface seen in a geographic tongue is shown. Note the hyper- and parakeratosis and the dense lymphocytic infiltration seen in the lamina propria. This picture is very reminiscent of psoriasis. (Right) High-power view shows the characteristic collections of neutrophils, called Munro microabscesses, within the epithelium. While this is a feature of psoriasis, most do not think the condition affects the oral cavity.



Munro Microabscesses



TERMINOLOGY

Synonyms

- Erythema migrans
- Benign migratory glossitis
- Psoriasiform mucositis

Definitions

- Benign inflammatory condition, primarily of tongue with unknown etiology

ETIOLOGY/PATHOGENESIS

Unknown

- Association with psoriasis
 - Severity appears correlated
- High association with fissured tongue
- Associated with atopy: Asthma and rhinitis
- Smoking appears protective
- Possible familial predisposition
- May be associated with hormone use
- Immunologic and psychologic factors may play factor

CLINICAL ISSUES

Epidemiology

- Incidence
 - 1-2.5% of population
- Age
 - Wide age range, most common in 2nd-3rd decades
- Sex
 - Female > male (1.5:1)

Site

- Primarily tongue: Tip, lateral borders, dorsal, and rarely ventral
- Rarely other oral mucosal sites: Buccal, labial, and soft palate

Presentation

- Usually asymptomatic
- Occasionally, burning sensation with food
 - Sour, spicy, and hot

Natural History

- Multiple, well-defined areas of erythema surrounded by raised, white-yellow borders that appear rapidly
- Healing occurs within days or weeks, then lesions develop in another area
- Lesions appear to move or migrate around surface of tongue

Treatment

- No treatment in nearly all cases
 - Reassure patient and explain condition
- Treatment rarely indicated except with severe burning sensation
 - Topical steroids and avoid trigger foods

Prognosis

- Excellent

MACROSCOPIC

General Features

- Areas of erythema
 - Represents atrophy of filiform papillae
- Raised white-yellow borders

MICROSCOPIC

Histologic Features

- Epithelium shows
 - Hyperparakeratosis
 - Spongiosis
 - Acanthosis
 - Elongated rete ridges
 - Munro microabscesses (collections of neutrophils in epithelium)
- Lamina propria
 - Lymphocytic infiltration
 - Neutrophilic infiltration
- Reminiscent of psoriasis

DIFFERENTIAL DIAGNOSIS

Candidiasis

- Fungal forms (hyphae and/or spores) within epithelium (often perpendicular)

Lichen Planus

- Band-like lymphocytic infiltrate
- Destruction of basal cell layer
- Degenerating keratinocytes

Lichenoid Mucositis

- Associations
 - Dental amalgam
 - Medications
 - Foods and oral hygiene products
- Band-like chronic inflammatory infiltrate

Psoriasis

- Exceedingly rare, considered by some not to affect oral cavity
- Correlation with skin disease

Contact Stomatitis

- Associated with cinnamon flavoring
 - Symptoms disappear with removal of causal agent
- Marked interface change with mixed inflammatory infiltrate
- Acanthosis with neutrophilic exocytosis

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Mucocele and Ranula

KEY FACTS

TERMINOLOGY

- Common lesion resulting from spillage of mucin into surrounding tissue from ruptured salivary gland duct

CLINICAL ISSUES

- More frequent in children and young adults
- Lower lip accounts for 70-81% of reported cases
- Mucocele: Chronic lesions require surgical excision
- Ranula: Marsupialization for superficial lesions
- Superficial mucocele most often occur on soft palate and retromolar area
 - Superficial mucoceles generally resolve in few days but often recur

MICROSCOPIC

- Normal overlying epithelium usually seen
- Mucin spillage surrounded by granulation tissue wall
- Adjacent glands exhibit chronic &/or sclerosing sialadenitis
- Adjacent ducts may show epithelial or oncocytic metaplasia

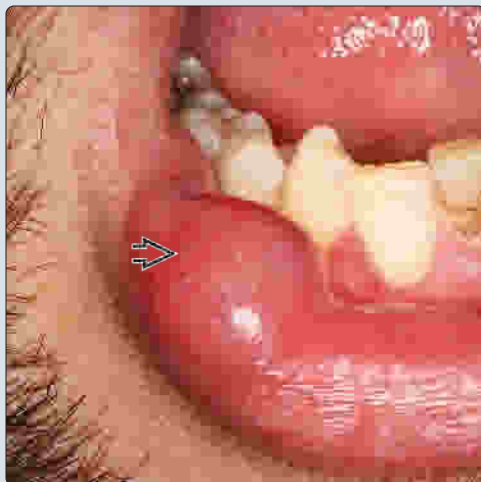
- Instead of mucin spillage, ectatic ducts may contain mucin plugs termed mucous retention phenomenon or salivary ductal ectasia
 - Dilated ducts may produce papillary foldings into duct lumen
 - When oncocytic metaplasia is present, these features are similar to Warthin tumor without lymphoid component

TOP DIFFERENTIAL DIAGNOSES

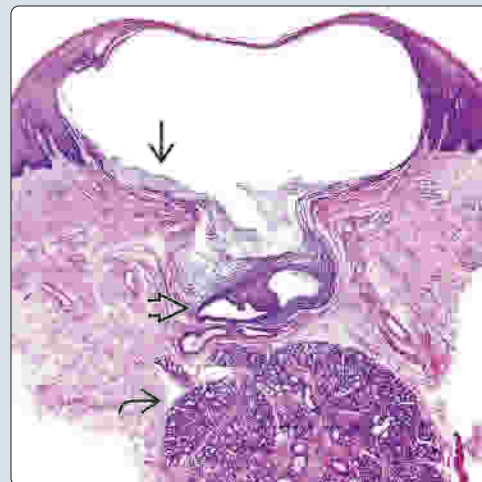
- **Mucous duct cyst**
 - Developmental, epithelial-lined cyst of uniform thickness
 - Lined by squamous, cuboidal, or columnar epithelium
 - Little to no inflammation is seen in cyst wall
- **Low-grade mucoepidermoid carcinoma**
 - Cyst lining not of uniform thickness
 - Careful examination of surrounding cyst usually shows more typical areas of mucoepidermoid carcinoma
 - Can be difficult on fine-needle aspiration if only mucinous material is withdrawn

Lower Lip Mucocele

(Left) Clinical photo shows a dome-shaped swelling on the lower lip, which is the most common location for a mucocele. Mucoceles are generally fluctuant, although older lesions may be firmer on palpation. Color ranges from mucosal to blue to red. (Right) Lower lip mucocele is seen with extravasated mucin in superficial lamina propria and epithelial atrophy. Adjacent metaplastic ducts and glands with chronic sialadenitis are seen in deeper lamina propria.

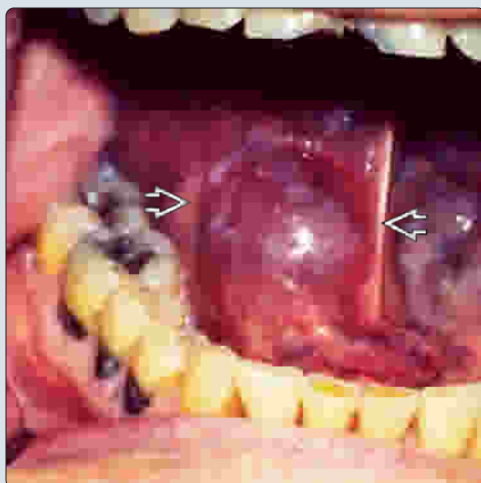


Mucocele With Extravasated Mucin



Ranula Presenting in Floor of Mouth

(Left) A blue, dome-shaped swelling in the floor of the mouth is the typical presentation of a ranula. The spilled mucin is usually of sublingual gland origin but can arise from the submandibular duct. Plunging ranulae occur when the spilled mucin dissects through the mylohyoid muscle resulting in a neck swelling. (Right) H&E shows a typical histology of a ranula from the floor of the mouth with inspissated mucin eliciting a prominent granulation tissue wall response. There is often no epithelial lining.



Granulation Response to Spilled Mucin



TERMINOLOGY

Synonyms

- Mucus escape reaction
- Mucus retention phenomenon

Definitions

- Common lesion resulting from spillage of mucin into surrounding tissue from ruptured salivary gland duct

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Most likely localized trauma to salivary gland ducts

CLINICAL ISSUES

Epidemiology

- Incidence
 - Common
- Age
 - More frequent in children and young adults
 - Peak incidence: 2nd decade

Site

- Mucocele
 - Lower lip accounts for 70-81% of reported cases
 - Floor of mouth, ventral tongue, and palate are less frequently seen
- Plunging ranula
 - Floor of mouth
- Superficial mucocele
 - Soft palate and retromolar area

Presentation

- **Mucocele**
 - Most common on lower lip
 - Frequently presents as dome-shaped swelling with blue coloration due to extravasated mucin
- **Superficial mucocele**
 - Single or multiple blisters
- **Ranula**
 - Swelling in floor of mouth with bluish coloration
 - Large lesions can elevate tongue
 - Plunging ranula result from mucin spillage dissecting mylohyoid muscle producing neck swelling

Natural History

- Most mucocèles and ranulae need to be excised
 - Superficial mucocèles generally resolve in few days but often recur

Treatment

- Surgical approaches
 - **Mucocèles**
 - Chronic unresolving lesions require surgical excision
 - Adjacent glands need to be removed to minimize recurrences
 - **Ranula**
 - Marsupialization used for superficial lesions
 - Sublingual gland excision needed for larger lesions

Prognosis

- No sequelae

MACROSCOPIC

Size

- **Mucocele**
 - Size ranges from few millimeters to > 1 cm
- **Superficial mucocele**
 - Usually 1-3 mm

MICROSCOPIC

Histologic Features

- Normal overlying epithelium usually seen
 - Surface ulceration may be present, particularly when mucocele has been secondarily traumatized
 - Extravasated mucin in superficial epithelium can be seen in superficial mucocèles
- Mucin spillage surrounded by granulation tissue wall
 - Inflammatory cells including foamy histiocytes are seen
 - Acute inflammation is not common feature
- Adjacent glands exhibit chronic &/or sclerosing sialadenitis
- Adjacent ducts may show epithelial or oncocytic metaplasia
- Instead of mucin spillage, ectatic ducts may contain mucin plugs termed mucous retention phenomenon or salivary ductal ectasia
 - Dilated ducts may produce papillary foldings into duct lumen
 - When oncocytic metaplasia is present, these features are similar to Warthin tumor without lymphoid component

DIFFERENTIAL DIAGNOSIS

Mucous Duct Cyst

- Developmental, epithelial-lined cyst of uniform thickness
- Can occur in both major and minor salivary glands
- Clinically similar to mucocèles
- Lined by squamous, cuboidal, or columnar epithelium
- Little to no inflammation is seen in cyst wall

Low-Grade Mucoepidermoid Carcinoma

- Clinically can mimic mucocele
- Cyst lining not of uniform thickness
- Mucous cells can be readily identified in cyst lining
- Careful examination of surrounding cyst usually shows more typical areas of mucoepidermoid carcinoma
- Can be difficult on fine-needle aspiration if only mucinous material is withdrawn

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Squamous Papilloma (Including Verruca and Condyloma)

KEY FACTS

TERMINOLOGY

- Benign squamous epithelial proliferation in exophytic-papillary pattern with branching fibrovascular tissue cores causally related to HPV infection

CLINICAL ISSUES

- Asymptomatic exophytic lesion that can occur anywhere, although most common in soft palate, uvula, hard palate, lingual frenum, tongue
- **SP**: Most common oral benign epithelial tumor
- **SP**: Peak: 30-50 years
- **VV**: Peak: Children or young adults
- **CA**: Peak: Young adults and teenagers
- Conservative excision, laser ablation, or cryotherapy

MICROSCOPIC


- **SP**: Finger-like projections of squamous epithelium overlying fibrovascular stroma, basal/parabasal hyperchromasia, upper spinous layer koilocytes

- **VV**: Multiple papillary projections with hypergranulosis, marked hyperkeratosis, elongated rete, which tend to converge toward center
- **CA**: Composed of acanthotic stratified squamous epithelium with papillary projections more blunted and broader than in squamous papilloma

TOP DIFFERENTIAL DIAGNOSES

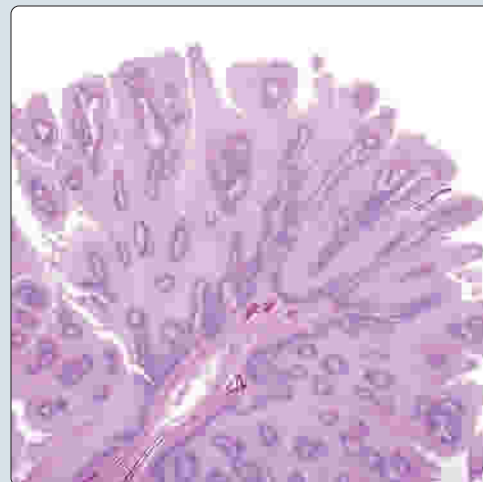
- **Proliferative verrucous leukoplakia**: Unrelenting progressive process that generally leads to conventional-type squamous carcinoma
- **Verrucous carcinoma**: Broad pushing border of infiltration at epithelial-stromal interface
- **Papillary squamous cell carcinoma**: Papillary projections lined by atypical to overtly malignant epithelium
- **Focal epithelial hyperplasia**: Scattered **mitosoid** cells
- **HIV-associated HPV papillomas**: Bizarre cellular atypia present in superficial spinous layer

Squamous Papilloma




(Left) Nonkeratinizing squamous papilloma of the soft palate is shown anterior to the tonsillar fauces . Papillomas may present as exophytic sessile lesions seen here or may be pedunculated. (Right) On low power, an exophytic benign papillary proliferation of stratified squamous epithelium surfaced by parakeratosis is seen. Multiple branching projections of edematous squamous epithelium are supported by fibrovascular core.



Papillary Projections in Squamous Papilloma

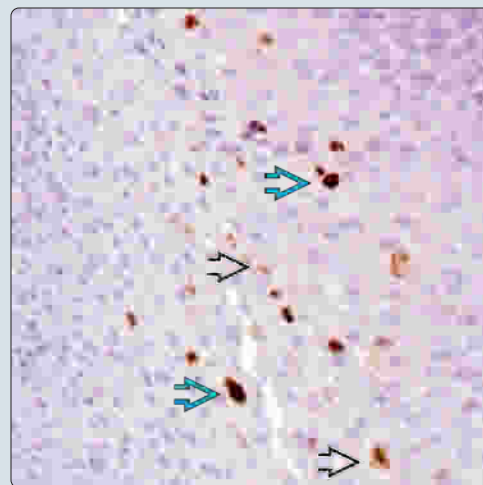


Fibrovascular Cores in Squamous Papilloma

(Left) High-power photomicrograph of squamous papilloma highlights the papillary fronds supported by fibrovascular cores . The surface keratin may be abundant as seen here, imparting a white appearance clinically. (Right) High-power image of a papillary frond shows diffuse in situ hybridization signals of low risk-HPV subtypes 6/11 within the nuclei, indicating episomal virus . Punctuate intranuclear in situ hybridization of HPV subtypes 6/11 signals indicate viral integration .



HPV Subtypes 6/11 In Situ Hybridization



TERMINOLOGY

Abbreviations

- Squamous papilloma (SP)
- Verruca vulgaris (VV)
- Condyloma acuminatum (CA)

Synonyms

- **VV**: Common wart, oral wart
- **CA**: Venereal wart

Definitions

- **SP**: Benign proliferation of squamous epithelium in exophytic pattern with branching fibrovascular tissue cores exhibiting papillary pattern causally related to human papillomavirus (HPV) infection
- **VV**: Benign, HPV-induced proliferation of squamous epithelium, usually on skin, but also in oral cavity
- **CA**: HPV-related proliferation of squamous epithelium of genitalia, perianal region, oral cavity, larynx

ETIOLOGY/PATHOGENESIS

Infectious Agents

- **SP**: HPV subtypes 6 and 11 have been detected in ~ 50% of cases
 - Virulence and infectivity rate thought to be low
 - Rarely HPV subtype 16 detected
- **VV**: HPV subtypes 2, 4, 6, 40, or 57 detected in up to 100% of cases
 - Contagious and can spread to various body parts by autoinoculation
- **CA**: Considered sexually transmitted disease
 - Lesions develop at site of contact or trauma
 - Usually HPV subtypes 2, 6, 11, 53, 54
 - Rarely high-risk HPV subtypes 16, 18, and 31 may be present (usually anogenital)
 - Oral CA may also arise from autoinoculation or maternal transmission

Pathogenesis

- HPV enters into epithelium at sites of trauma or wounds and infects actively dividing basal cells
- Viral altered epithelial cells in spinous layer (koilocytes)

CLINICAL ISSUES

Epidemiology

- Incidence
 - **SP**: Considered most frequent benign epithelial tumor of oral cavity
 - **VV**: Uncommon in oral cavity
 - **CA**: Uncommon in oral cavity
- Age
 - **SP**: Peak: 30-50 years but can affect all age groups
 - **VV**: More frequently seen in children or young adults
 - **CA**: Generally diagnosed in young adults and teenagers
 - Vertical transmission from mother to infant have been reported
 - CA in young children may represent sexual abuse
- Sex
 - **SP and VV**: Equal gender distribution

Site

- **SP**: May occur anywhere but most common sites include soft palate, gingiva, hard palate, lingual frenum, and tongue
- **VV**: Oral lesions mostly occur on vermillion border, tongue, and labial mucosa
- **CA**: Oral lesions most frequently seen in soft palate, lingual frenum, and labial mucosa

Presentation

- **SP**
 - Usually presents as asymptomatic exophytic, pedunculated, or sessile lesion
 - Color: White, red, or mucosal-colored depending on amount of surface keratinization
 - Generally ≤ 5 mm although can be larger
 - Spike-like or finger-like projections
 - Papillary projection can be blunted, imparting cauliflower appearance
- **VV**
 - Asymptomatic
 - Can be sessile or pedunculated
 - Oral: Generally white
 - Generally ≤ 5 mm
 - Symmetrical round to ovoid papule or nodule with rough pebbly surface with central area of hyperkeratosis
 - Well demarcated with abrupt margins
- **CA**
 - Generally sessile and mucosal-colored asymptomatic lesion
 - Multiple lesions often coalesce, forming larger mass
 - Generally 1-1.5 cm, although can be larger
 - Papillary projections are more blunted

Natural History

- Squamous papilloma and verruca vulgaris may spontaneously regress

Treatment

- Surgical approaches
 - Conservative surgical excision
 - Laser ablation
 - Cryotherapy: Forms subepithelial blister leading to sloughing of lesion
- Drugs
 - Typical cutaneous treatments (intralesional bleomycin and 5-fluorouracil) **not** used for oral VV
 - Intralesional and topical cidofovir used for CA

Prognosis

- **Squamous papilloma and verruca vulgaris**
 - Recurrences have been reported
 - Some lesions will spontaneously resolve
- **Condyloma acuminatum**
 - No malignant transformation reported in oral CA, unlike anogenital area

MACROSCOPIC

General Features

- Depends on type of lesion
- Sessile, exophytic to pedunculated mass

Squamous Papilloma (Including Verruca and Condyloma)

- Rough pebbly surface to multiple finger-like papillary projections, sometimes blunted

MICROSCOPIC

Histologic Features

- **Squamous papilloma**
 - Finger-like projections
 - Thin, fibrovascular cores lined by squamous epithelium
 - Basal and parabasal hyperchromasia
 - Increased mitotic activity may be observed; is not indicator for dysplasia or malignancy
 - **Koilocytes** can be seen in prickle (spinous) layer
 - Hyperchromatic nucleus with wrinkled appearance
 - Perinuclear clearing
 - Well-defined, prominent intercellular borders
- **Verruca vulgaris**
 - Broad flat base
 - Multiple papillary projections with prominent granular layer (hypergranulosis) and marked hyperkeratosis
 - Coarse keratohyaline granules
 - Lack of branching of fibrovascular cores
 - Elongated rete ridges, which tend to converge toward center
 - Koilocytes noted in superficial spinous layer
- **Condyloma acuminatum**
 - Acanthotic stratified squamous epithelium with papillary fronds
 - Projections more blunted and broader than in squamous papilloma
 - Appearance of keratin-filled crypts between projections into spinous layer
 - Rete ridges often bulbous
 - Variable number of koilocytes in prickle layer
 - Not as common in oral CA compared to anogenital lesions
 - Surface keratinization less than in VV and most oral SP
 - Underlying excretory ducts of minor salivary glands may be involved
 - Need to distinguish from salivary ductal papillomas

ANCILLARY TESTS

In Situ Hybridization

- Reliable method in paraffin-embedded tissue using type-specific probes
 - Not generally useful for diagnosis, treatment planning, or prognosis
 - Both episomal and integrated HPV is identified

PCR

- Most sensitive method for HPV detection and subtyping
 - Generally used only in research settings

DIFFERENTIAL DIAGNOSIS

Proliferative Verrucous Leukoplakia

- Lesions are multifocal and widespread
- Histologically variable
 - Early lesions may exhibit abundant keratosis with verrucous or papillary surface
 - Marked acanthosis

- Dysplasia not a feature in early lesions
- Unrelenting progressive process that generally leads to conventional type squamous cell carcinoma

Verrucous Carcinoma

- Larger lesion
- Broad pushing border of infiltration at epithelial-stromal interface
- Marked parakeratosis with parakeratotic crypting and church-spire keratosis
- Normal epithelial maturation
- Occasional normal mitotic figure can be present in basal &/or parabasal layer
- No koilocytes

Papillary Squamous Cell Carcinoma

- Papillary projections lined by atypical to overtly malignant epithelium
- Hypercellular tumor
- Abnormal epithelial maturation
- Cellular pleomorphism
- Increased mitoses, including atypical mitotic figures
- Stromal invasion may or may not be seen

Focal Epithelial Hyperplasia (Heck Disease)

- Disease presents as multiple lesions generally in children and young adults
- Abrupt epithelial acanthosis
- Usually does not have papillary surface
- Elongated, broad rete ridges
- Scattered **mitosoid** cells
 - Altered nucleus resembling a mitotic figure

HIV-Associated HPV Papillomas

- Usually multiple lesions
 - Present as mucosal-colored papules, cauliflower-like growths, or keratotic papillary projections
- Bizarre cellular atypia present in superficial spinous layer
 - Large pleomorphic nuclei and scattered giant cells
- Basal and parabasal layers generally unaffected
- Scattered koilocytes
 - HPV-7 and HPV-32 have been isolated
- Malignant transformation has not been reported

DIAGNOSTIC CHECKLIST

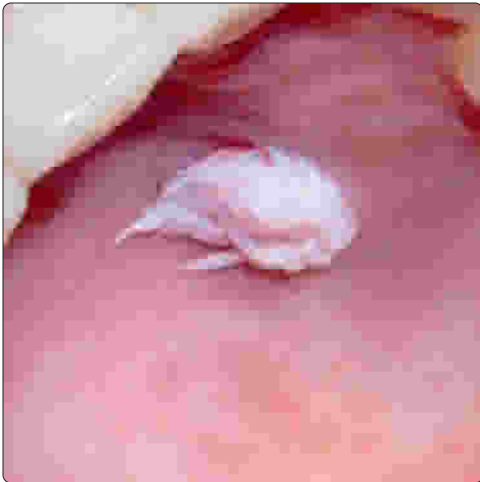
Clinically Relevant Pathologic Features

- Nuclear features
 - Presence of koilocytes supports viral etiology

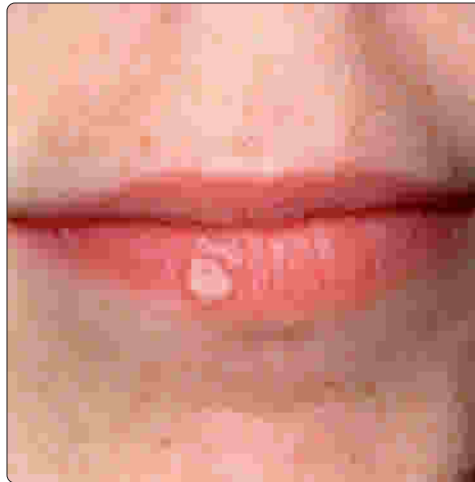
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Clinical Photo of Keratinized Squamous Papilloma



Clinical Photo of Lip Verruca Vulgaris

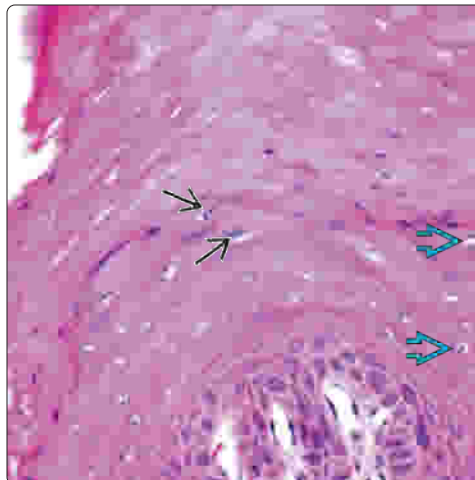


(Left) Squamous papilloma of the hard palate presents as a pedunculated lesion with numerous spike-like keratotic projections imparting a warty appearance. Depending on the degree of keratinization, squamous papilloma can be white, red, or mucosal color. (Right) Verruca vulgaris of the lower lip in a child is shown. The vermilion border is a common location for verruca, which exhibits a rough, papillary surface. Verruca can also have papillary projections similar to squamous papillomas.

Hyperkeratotic Epithelium in Verruca Vulgaris

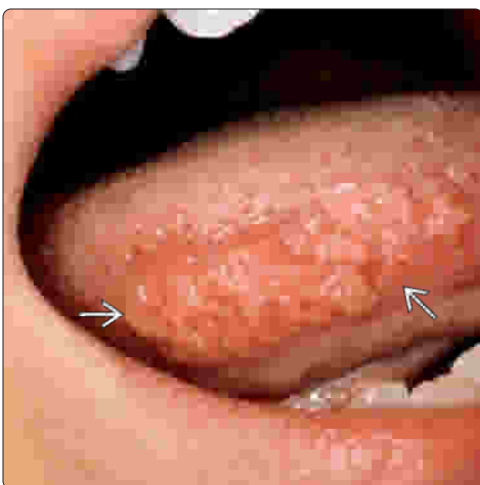


Keratohyaline Granules in Verruca Vulgaris



(Left) Verruca vulgaris exhibits numerous papillary projections surfaced by a markedly keratotic squamous epithelium with a broad flat base with elongated rete ridges that converge toward the center of the lesion. (Right) High-power view of a verruca vulgaris shows coarse keratohyaline granules in the superficial spinous layer characterized by dark, condensed nuclei with cytoplasmic clearing. Scattered koilocytes can also be identified.

Clinical Photo of Condyloma Acuminatum



Blunted Papillary Projections of Condyloma Acuminatum



(Left) Oral condyloma acuminatum of the lateral tongue presents as a pink, broad-based, sessile lesion with blunted surface projections. The lesions are usually well demarcated from the surrounding normal tissue and may be multiple. (Right) Typical appearance of condyloma exhibits broader and more blunted papillary projections than squamous papillomas. The epithelium is markedly acanthotic. Koilocytes may be seen in the spinous layer but are more sparse than in genital condyloma.

Granular Cell Tumor

KEY FACTS

TERMINOLOGY

- Benign tumor composed of poorly demarcated accumulation of plump granular cells
- Thought to arise from Schwann cells
 - Granules represent senescent change with accumulation of autophagocytic lysosomes

CLINICAL ISSUES

- Male < female (1:3)
- Black people affected more often than white people
- Up to 70% of head and neck lesions develop in oral cavity (tongue most common)
- Up to 20% of patients will have multifocal disease
- Recurrence/relapse/persistence is uncommon (~ 10%)
- Tongue is most common single site (> 50% of all head and neck cases)
- Complete excision with narrow margins yields best outcome

MACROSCOPIC

- Cut surface is firm, pale yellow or cream
- Mean: 1-2 cm; range up to 3 cm

MICROSCOPIC

- Unencapsulated plump, polygonal to elongated granular cells blending with adjacent soft tissues, especially skeletal muscle
- Indistinct cell membranes surround abundant, granular, eosinophilic cytoplasm
- Overlying pseudoepitheliomatous hyperplasia is common


ANCILLARY TESTS

- Granules are PAS **positive**, diastase resistant
- Strongly and uniformly **positive** for S100 protein

TOP DIFFERENTIAL DIAGNOSES

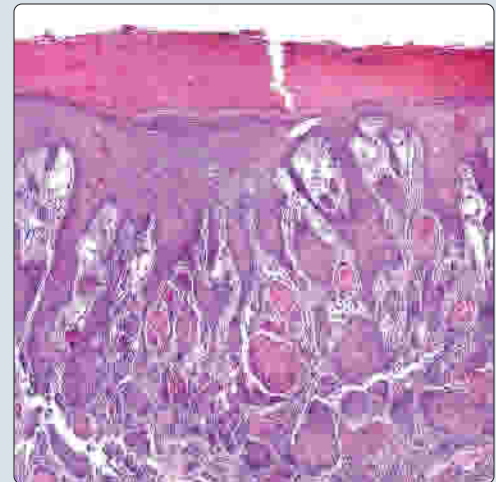
- Squamous cell carcinoma, rhabdomyoma, congenital epulis of newborn, schwannoma, alveolar soft part sarcoma, leiomyoma, lichen planus reaction

Lateral Tongue Submucosal Mass

(Left) Granular cell tumors present clinically as either a smooth-surfaced, submucosal swelling or nodule or as a pale to white, discrete, plaque-like lesion . (Right) Remarkably prominent pseudoepitheliomatous hyperplasia (PEH) is noted overlying and intimately associated with a granular cell tumor. The tumor is unencapsulated, blended imperceptibly with the PEH.

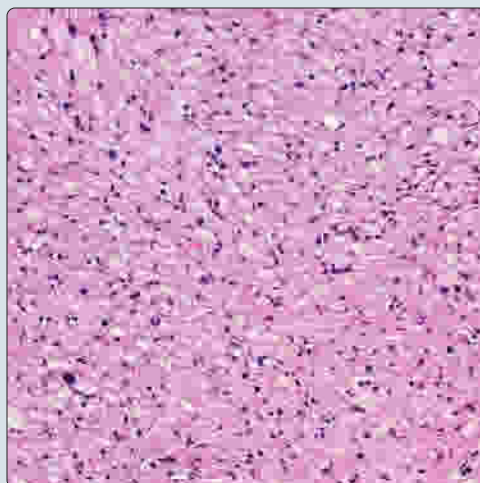


Marked PEH

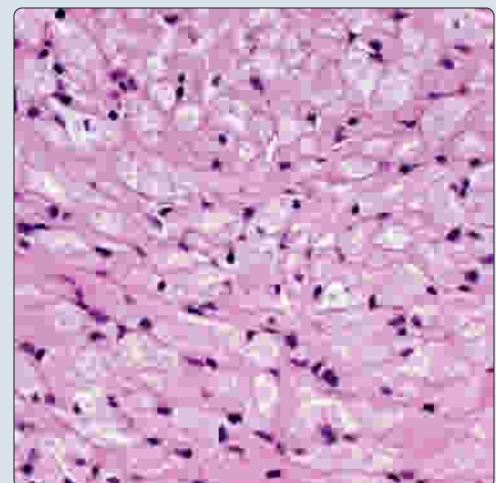


Polygonal Granular Cells

(Left) There is a vaguely fascicular arrangement to these polygonal granular cells. Note the abundant granular cytoplasm. The nuclei are small with a hyperchromatic appearance from this intermediate power. (Right) The granular cells are polygonal, showing a slightly spindled appearance. The cytoplasm contains numerous eosinophilic granules. The nuclei are small, round to oval, and hyperchromatic.



Polygonal Granular Cells



TERMINOLOGY

Abbreviations

- Granular cell tumor (GCT)

Synonyms

- Granular cell myoblastoma
- Abrikossoff tumor

Definitions

- Benign tumor composed of poorly demarcated accumulation of plump granular cells
 - Distinct from congenital epulis of newborn (gingival granular cell tumor of infancy)

ETIOLOGY/PATHOGENESIS

Schwann Cell Derivation

- Thought to arise from Schwann cells
 - Positive with neural-associated antibodies
 - Granules represent senescent change with accumulation of autophagocytic lysosomes

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare, < 1% of all head and neck tumors
- Age
 - All ages, but peak between 40 and 60 years
- Sex
 - Male < female (1:3)
- Ethnicity
 - Black people affected more often than white people

Site

- Over 50% of GCTs involve head and neck
 - Up to 70% of these develop in oral cavity (tongue, lips, buccal mucosa, floor of mouth, hard palate)
- Tongue is most common single site (> 50% of all head and neck cases)
 - Dorsum >> lateral margin
- Up to 20% of patients will have multifocal disease (oral or other sites)

Presentation

- Most present as painless, pale mass; present for < 12 months
- Rarely, may present with Eagle syndrome
 - Elicitation of pain on swallowing, turning head, or extending tongue
 - Syndrome is thought to be caused by irritation of glossopharyngeal nerve
- Occasionally, there are concurrent candidal infections

Treatment

- Surgical approaches
 - Complete excision with narrow margins yields best outcome

Prognosis

- Excellent long-term prognosis
- Recurrence/relapse/persistence is uncommon (~ 10%)

- Malignant GCTs very rare in oral cavity

MACROSCOPIC

General Features

- Smooth-surfaced, poorly demarcated submucosal swelling or nodule
- Cut surface has firm texture, pale yellow or cream
- Concurrent candidal infection may create discrete, white plaque

Size

- Mean: 1-2 cm; range up to 3 cm

MICROSCOPIC

Histologic Features

- Nonencapsulated
 - Blending with adjacent soft tissues, especially skeletal muscle, is common
 - May extend up to epithelium, specifically papillae
 - Satellite nodules can develop
- Plump, polygonal to elongated eosinophilic cells
- Indistinct cell membranes, creating syncytium
- Abundant, granular eosinophilic cytoplasm (filled with lysosomes)
- Contain central small, dark to vesicular nuclei
- Overlying pseudoepitheliomatous hyperplasia (PEH)
 - Usually limited to epithelium immediately overlying tumor
 - Seen in ~ 30% of cases
- Rarely, marked stromal desmoplasia may be seen

ANCILLARY TESTS

Frozen Sections

- Pseudoepitheliomatous hyperplasia can mask tumor
- Granular, eosinophilic cytoplasm is usually easy to detect

Histochemistry

- Granules are PAS positive, diastase resistant

Immunohistochemistry

- Strongly and uniformly **positive** for S100 protein (nuclear and cytoplasmic) and SOX10 (nuclear)

Electron Microscopy

- Myelin-like figures, axon-like structures, angulate bodies, and basal lamina

DIFFERENTIAL DIAGNOSIS

Squamous Cell Carcinoma

- PEH can mimic squamous cell carcinoma
 - PEH is only associated with GCT; it is not tumor itself
- Small, superficial-surface biopsy specimens can be difficult; must be properly oriented
- Squamous cell carcinoma usually shows p53 and E-cadherin immunoreactivity, findings not seen in PEH

Rhabdomyoma (Adult or Fetal)

- Uncommon in oral cavity
- Shows sheet-like distribution of polygonal cells with homogeneous, eosinophilic cytoplasm; lacks PEH

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
S100	Positive	Nuclear & cytoplasmic	Nearly all tumor cells
SOX10	Positive	Nuclear	Strong, diffuse, nuclear positive
CD68	Positive	Cytoplasmic	Schwann cells of GCT (normal Schwann cells negative)
Vimentin	Positive	Cytoplasmic	Strong and diffuse in all tumor cells
NSE	Positive	Cytoplasmic	Weak to strong in most tumor cells
CD57	Positive	Cytoplasmic	Weak reaction but in nearly all tumor cells
PGP9.5	Positive	Cytoplasmic	Most tumor cells
Inhibin-α	Positive	Cytoplasmic	Variably positive in most tumor cells
Calretinin	Positive	Nuclear & cytoplasmic	Variable in most tumor cells
p75	Positive	Cell membrane	Most tumor cells
GFAP	Negative		
CK-PAN	Negative		
α-1-antitrypsin	Negative		
Desmin	Negative		Seen in rhabdomyoma
GLUT1	Negative		Not associated with perineural cells
TFE3	Negative		Seen in alveolar soft part sarcoma

GCT = granular cell tumor.

- Cytoplasmic clearing with "spiderweb" cells is characteristic
- PTAH highlights cytoplasmic cross striations; **positive**: Desmin, myoglobin, myogenin

Congenital Epulis of Newborn

- Can be histologically indistinguishable from GCT but develops in newborns to infants **only**
- **Positive**: Vimentin, NSE; **negative**: S100 protein, SOX10

Nonneural Granular Cell Tumor

- Identical histologically, although occasionally with more cytologic atypia, but seen in **adults** not newborns
- **Negative**: S100 protein, SOX10

Schwannoma

- Often encapsulated, with well-defined border, showing Antoni A and Antoni B areas, with Verocay bodies and more spindled arrangement
- Not associated with PEH
- **Positive**: S100 protein, SOX10, capsular EMA; **negative**: CD68

Alveolar Soft Part Sarcoma

- Solid nodules of tumor separated by thin vascularized septa into organoid or alveolar nests
- Large polygonal cells with eosinophilic, granular cytoplasm, vesicular nuclei, and cytoplasmic crystalloids
- **Positive**: TFE3 nuclear, CD68, NSE; **negative**: S100 protein, desmin, pancytokeratin
 - *ASPCR1/TFE3* fusion transcript results from t(X;17)(p11;q25) translocation

Leiomyoma

- Uncommon in oral cavity
- Short to long, sweeping and interlacing fascicles of spindled cells, lacking granular cytoplasm

- **Positive**: Actin-sm, actin-HHF-35, desmin; **negative**: S100 protein

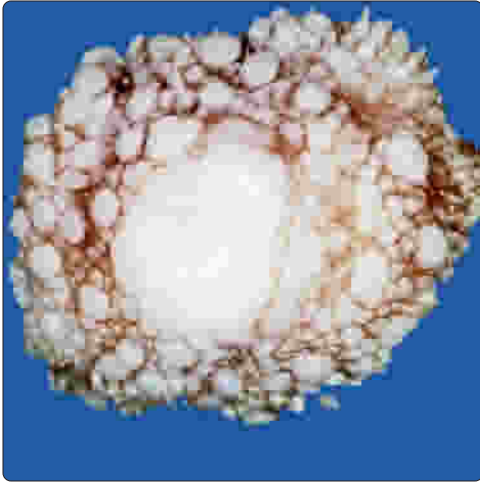
Lichen Planus Reaction

- Significant granular cells can be seen in association with oral lichen planus
 - Also called oral ceroid granuloma
- Characteristic interface inflammatory infiltrate with Civatte bodies
- Direct immunofluorescence characteristic for lichen planus
- Cells are **positive** with S100 protein
 - Thought to be reactive phenomenon triggered by inflammatory infiltrate
- Simultaneous presence of GCT and oral lichen planus may be possible

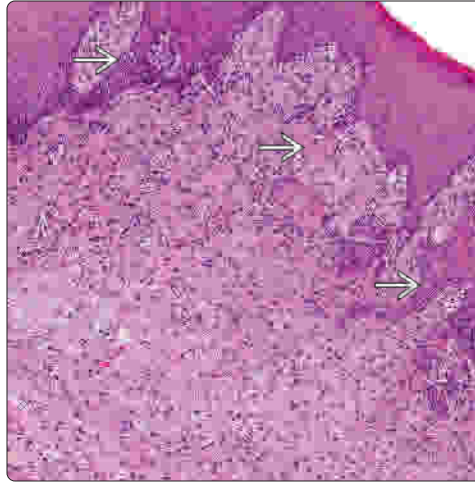
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Gross Photograph of Granular Cell Tumor

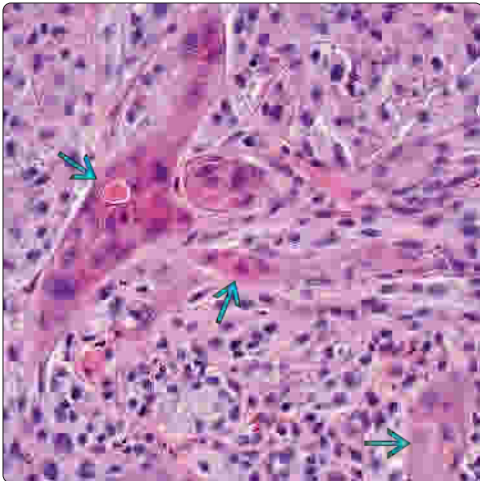


PEH Overlying Granular Cell Tumor

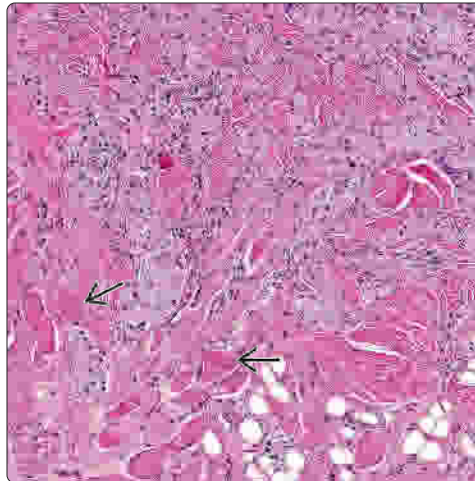


(Left) This macroscopic photograph shows a smooth-surfaced, submucosal nodule, yielding a pale appearance. Note the remarkable number of papillary projections, part of concurrent PEH. (Right) Prominent PEH is noted overlying this granular cell tumor. The tumor is unencapsulated, creating a sheet-like distribution of neoplastic granular cells. The PEH is usually limited to the lateral extent of the tumor.

Blending of PEH With Granular Cell Tumor

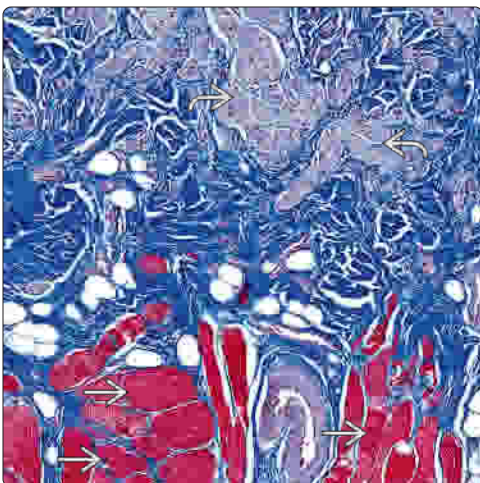


Granular Cell Tumor Involving Tongue Muscle

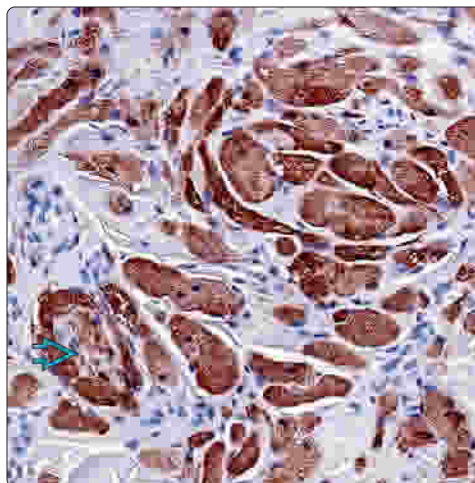


(Left) There is a very intimate blending of the surface PEH with the granular cell tumor cells. In superficial biopsies, the separation may be quite challenging. (Right) The granular cell tumor cells can be seen deep in the sample, blending with the adjacent skeletal muscle fibers and adipose tissue. The skeletal muscle may become atrophic, mimicking granular cells.

Trichrome Differential Staining in Granular Cell Tumor



S100 Protein Strongly Highlights Tumor Cells



(Left) A number of special stains may be of value in separating between soft tissue lesions of the oral cavity. A trichrome stains the skeletal muscle brightly eosinophilic (red), while the fibrous connective tissue is blue. Note that the granular cells are lighter blue. (Right) S100 protein strongly stains the cytoplasm and the nuclei of the granular cells. Note the entrapped peripheral nerve. The tumor is derived from Schwann cells, so nerve association is common.

Congenital Granular Cell Epulis

KEY FACTS

TERMINOLOGY

- Rare, benign congenital growth on alveolar mucosa in neonates

CLINICAL ISSUES

- Female >> male (8-10:1)
- Maxilla >> mandible (3:1)
- Clinically presents at birth to within a few weeks
- Smooth-surfaced pink to red polypoid mass
- Lesions appear to regress after birth
- Surgical excision under anesthesia
- Recurrences have not been reported even after incomplete excision
- No reports of malignant transformation

MICROSCOPIC

- Stroma is composed of sheets of large polygonal cells
 - Abundant eosinophilic granular cytoplasm
 - Small round or oval basophilic nuclei

- Overlying epithelium is uniform in thickness
- Older lesions may have fibrous septa with granular cells arranged in clusters

ANCILLARY TESTS

- **Immunohistochemistry**
 - **Positive:** Vimentin, CD68
 - **Negative:** S100 protein, SOX10, cytokeratin, actin, desmin, estrogen and progesterone receptors
- **Electron Microscopy**
 - No evidence of schwannian or epithelial differentiation

TOP DIFFERENTIAL DIAGNOSES

- Granular cell tumor
 - Has pseudoepitheliomatous hyperplasia
 - **Positive:** S100 protein, SOX10

DIAGNOSTIC CHECKLIST

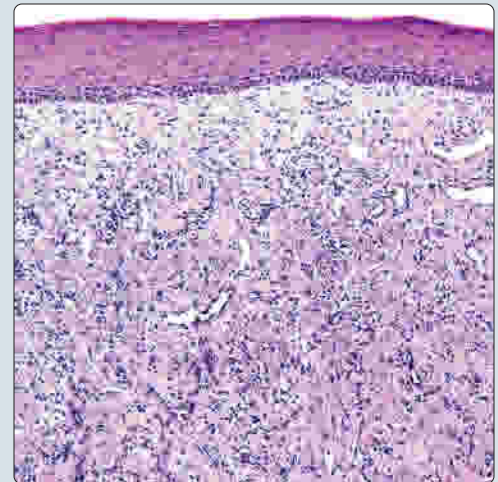
- S100 protein (-) granular cells in soft tissue mass on alveolus of neonate are pathognomonic for congenital epulis

Clinical Photo of Gum Congenital Epulis


(Left) Congenital epulis shows a red polypoid mass in the mandibular alveolus of a newborn. Most cases are ≤ 2 cm in size, and more than 90% develop in female patients. **(Right)** A low-power microscopic image of a congenital epulis shows that the epithelium of the congenital epulis is uniform and lacks rete ridges. Unlike granular cell tumors, pseudoepitheliomatous hyperplasia (PEH) is not present.

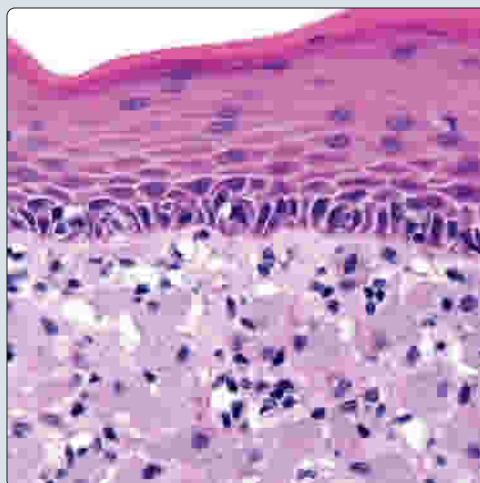


Uniform Epithelium Lacking PEH

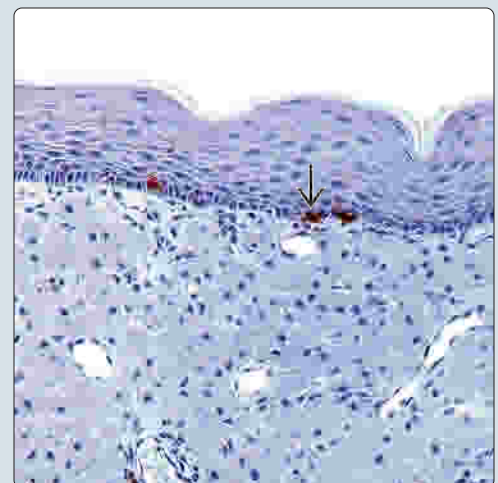


Large Polygonal Granular Cells

(Left) High-power photomicrograph of a congenital epulis shows a uniform epithelium with atrophy of the rete ridges. Cells with abundant granular cytoplasm and basophilic nuclei are seen in the lamina propria. **(Right)** Unlike the granular cell tumor, the granular cells in congenital epulis are not immunoreactive for S100 protein (or SOX10). The overlying epithelium shows isolated melanocytes  positive with S100 protein as an internal control.



Negative for S100 Protein



TERMINOLOGY

Synonyms

- Congenital epulis of newborn
- Gingival granular cell tumor of infancy

Definitions

- Rare, benign congenital growth on alveolar mucosa in neonates

ETIOLOGY/PATHOGENESIS

Etiology

- Uncertain etiology, but possible nerve derivation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very rare
 - Estimated to be ~ 0.0006%
- Age
 - Neonates
- Sex
 - Female >> male (8-10:1)

Site

- Gingival mucosa of maxilla or mandible
 - Maxilla >> mandible (3:1)
- Rare reports described on the tongue

Presentation

- Clinically presents at birth or within a few weeks
 - Some cases have been detected in utero by ultrasound
- Frequently occurs just lateral to midline in canine/lateral incisor region
- Smooth-surfaced pink to red polypoid mass
- Can cause respiratory obstruction
- Can cause feeding difficulties
- Generally presents as solitary mass
 - 10% of cases occur as multiple lesions

Natural History

- Lesions appear to regress after birth
- Rare: Complete regression without treatment

Treatment

- Surgical excision under local or general anesthesia

Prognosis

- Recurrences have not been reported even after incomplete excision
- No reports of malignant transformation

IMAGING

MR Findings

- Homogeneous mass without enhancement on T1WI
 - Generally excludes vascular lesion
- Mass appears to arise from alveolus with no bone extension

MACROSCOPIC

General Features

- Polypoid mass
- Color ranges from pink to red

Size

- Usually ≤ 2 cm
 - Reports of lesions up to 9 cm

MICROSCOPIC

Histologic Features

- Overlying epithelium is uniform in thickness, lacking rete ridges
- Stroma is composed of sheets of large polygonal cells
 - Abundant eosinophilic granular cytoplasm
 - Small round or oval basophilic nuclei
- Small capillaries can be seen
- Older lesions may have fibrous septa with granular cells arranged in clusters

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** Vimentin, CD68
- **Negative:** S100 protein, SOX10, cytokeratin, actin, desmin, estrogen and progesterone receptors

Electron Microscopy

- Granular cytoplasm shows heterogeneous electron-dense granules, lysosomes, and lipid droplets
- Cells have irregular cytoplasmic borders
- No evidence of schwannian or epithelial differentiation

DIFFERENTIAL DIAGNOSIS

Clinical DDx

- Melanotic neuroectodermal tumor of infancy
 - Midline lesion that shows melanin pigmentation
- Hemangiomas and vascular malformations
 - Usually red to blue-red in color
 - Ultrasonography findings can distinguish between the 2 entities
- Lymphatic malformations
 - Compressible mass, diagnosed by ultrasound

Granular Cell Tumor

- Has pseudoepitheliomatous hyperplasia
- **Positive:** S100 protein, SOX10

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Microscopic features of S100 protein (-) granular cells in soft tissue mass on alveolus of neonate are pathognomonic for congenital epulis

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Pyogenic Granuloma

KEY FACTS

TERMINOLOGY

- Common, nonneoplastic polypoid growth of oral cavity

ETIOLOGY/PATHOGENESIS

- Poor oral hygiene
- Localized trauma (biting)

CLINICAL ISSUES

- Female predilection
- ~ 1% of pregnant women develop pyogenic granuloma (PG)
- Pediatric age (up to 18 years): Male > female
- ~ 75% of oral cavity PG occur on gingiva
- Lips, tongue, and buccal mucosa are common sites
- Generally painless lobulated or polypoid mass
- Color varies with age of lesion
 - Earlier lesions tend to be highly vascular and will be purple to red
- Surface ulceration and bleeding



MICROSCOPIC

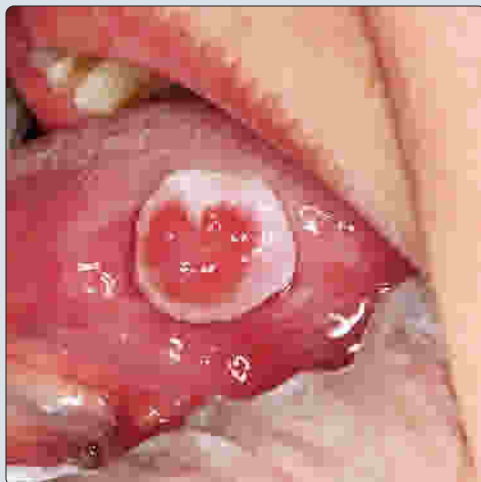
- Surface ulceration
- Below area of ulceration, mixed inflammation of neutrophils, lymphocytes, and plasma cells
- Small and large vessels often organized in lobular arrangement separated by fibrous septa
- Vessels often are engorged with red blood cells
- Early lesions may have frequent but not atypical mitoses
- Older lesions appear more collagenized

TOP DIFFERENTIAL DIAGNOSES

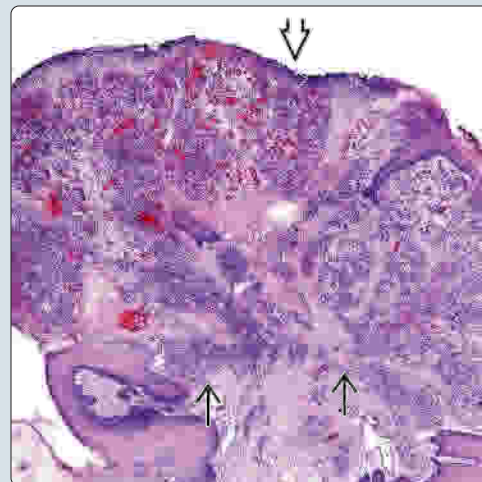
- **Clinical mimics:** Peripheral ossifying fibroma, peripheral giant cell granuloma
 - All occur on gingiva and can become secondarily ulcerated
 - Microscopically these 3 lesions are distinct
- **Kaposi sarcoma:** Atypical mitoses and hyaline eosinophilic globules
- **Angiosarcoma:** Rare in oral cavity

Pyogenic Granuloma



(Left) Typical clinical appearance of pyogenic granuloma (PG) occurring on the lateral border of the tongue is shown. The lesion is exophytic and likely to become secondarily traumatized by biting. Note the central area of erythema, which corresponds to ulceration. **(Right)** Low-power photomicrograph of an ulcerated  pyogenic granuloma illustrates polypoid nature of the lesion as well as the zonal pattern of inflammation. The typical lobular pattern is more evident at the base .

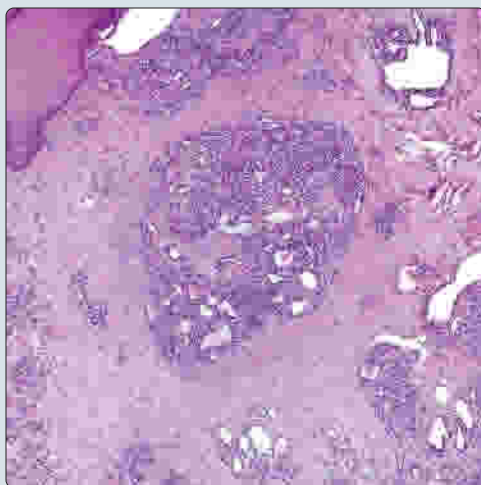


Surface Ulceration Overlying Lobular Vascular Pattern

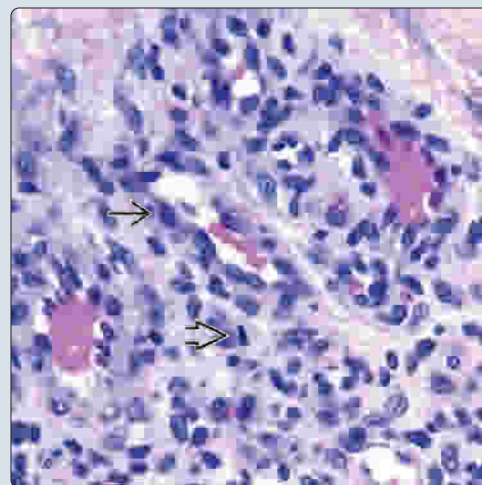


Lobular Configuration

(Left) A lobular proliferation of small and large endothelial-lined channels (surrounded by connective tissue) is noted. With age, both intralobular and perilobular fibrosis occurs and less secondary inflammation is present in the stroma. **(Right)** Mitoses  can be seen in pyogenic granulomas, especially early lesions; however, atypical mitoses are not seen. Endothelial cells can be plump with an epithelioid appearance . Intraluminal red blood cells are a common finding.



Early Lesions May Have Mitotic Figures



TERMINOLOGY

Abbreviations

- Pyogenic granuloma (PG)

Synonyms

- Lobular capillary hemangioma
- Pregnancy tumor (epulis gravidarum)

Definitions

- Benign overgrowth of capillary loops with obviously vascular phenotype

ETIOLOGY/PATHOGENESIS

Etiology

- Poor oral hygiene
- Local irritants: Fractured tooth, poor restoration
- Localized trauma (biting)
- Hormones
 - Increased in pregnancy or oral contraceptive use

Pathogenesis

- Bicellular origin from endothelial and pericytic cells

CLINICAL ISSUES

Epidemiology

- Incidence
 - Common throughout world
- Age
 - Wide range
 - Most common: Children and young adults
- Sex
 - Female > male (2:1)
 - ~ 1% of pregnant women develop PG
 - Pediatric age (up to 18 years): Male > female

Site

- Gingiva
 - Most common (75%) site of oral cavity PG
 - Maxillary gingiva > mandibular gingiva
 - Anterior > posterior
 - Facial area > lingual or palatal gingiva
 - Some lesions however may extend from facial aspect to lingual or palatal tissue
 - Usual site in pregnant women
- Lips, tongue, and buccal mucosa are common sites
- Extraction socket (epulis granulomatosa)

Presentation

- Generally painless lobulated or polypoid mass
- Early lesions tend to be highly vascular and will be purple to red
- Older lesions become more fibrotic and appear pink
- Surface ulceration and bleeding
- Exuberant overgrowth of granulation tissue arising in recent extraction site
 - May be associated with sequestrum

Natural History

- PG incidence increases throughout pregnancy
 - Can spontaneously resolve after childbirth

Treatment

- Surgical approaches
 - Conservative excision, down to periosteum
- Remove inciting factor
 - Scaling of teeth and improve oral hygiene

Prognosis

- Occasionally lesion recurs
 - PG removed during pregnancy often recurs
 - Recurrences more common in children

MACROSCOPIC

General Features

- Polypoid (pedunculated), nodular, or lobular soft and compressible mass often with surface ulceration
- May be connected by stalk

Size

- Range: 0.3-8 cm

MICROSCOPIC

Histologic Features

- Surface ulceration
 - Collarette of epithelium around ulcerated area
- Thickened fibrinopurulent membrane
- Below area of ulceration, mixed inflammation of neutrophils, lymphocytes, and plasma cells
 - Inflammation greater near surface and less at center
- Small and large vessels often organized in lobular arrangement separated by fibrous septa
 - When ulceration is present, this finding seen in deeper portion of lesion
 - Lumina can be absent, slit-like to prominent
 - Endothelial cells range from plump to flattened
 - Small capillaries and venules arranged around central vessel
- Vessels often are engorged with red blood cells
- Mitotic activity variable
 - Early: May have frequent but not atypical mitoses
- Older lesions appear more collagenized

DIFFERENTIAL DIAGNOSIS

Clinical Mimics

- Peripheral ossifying fibroma; peripheral giant cell granuloma
- All occur on gingiva and can become secondarily ulcerated
- Microscopically these 3 lesions are distinct

Kaposi Sarcoma

- Atypical mitoses and hyaline eosinophilic globules

Angiosarcoma

- Rare in oral cavity

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Peripheral Giant Cell Granuloma

KEY FACTS

TERMINOLOGY

- Reactive proliferation of multinucleated giant cells caused by trauma or irritation

CLINICAL ISSUES

- Common
- Exclusive to gingiva
- Often ulcerated
- Slight female predilection
- Wide age range with peak in 5th and 6th decades
- Treatment is excision down to underlying bone
- Recurrence rate is ~ 10%
- Wide range, peak is 40-60 years of age

IMAGING

- Rarely, "cupping" resorption of underlying bone (usually seen intraoperatively)
- Should not have intraosseous component


MICROSCOPIC

- Proliferation of multinucleated giant cells
- Epithelium is frequently ulcerated
- Stroma
 - Plump to ovoid cells
 - Hemorrhage (interstitial)
 - Hemosiderin pigment deposition

TOP DIFFERENTIAL DIAGNOSES

- Peripheral ossifying fibroma
- Pyogenic granuloma
- Fibroma
- Central giant cell lesion
 - Central giant cell granuloma
 - Brown tumor of hyperparathyroidism
 - Giant cell tumor
 - Cherubism

Nodule of Anterior Mandible



(Left) Clinical photograph of a young child shows a sessile, nodular, red-blue mass of the mandibular gingiva. As demonstrated in this photo, the mandibular gingiva is often affected. (Right) Hematoxylin and eosin shows a low-power view of an exophytic soft tissue mass excised from the anterior mandibular gingiva. The epithelium  can be seen on the surface of this lesion, and an ulcer is a common finding.

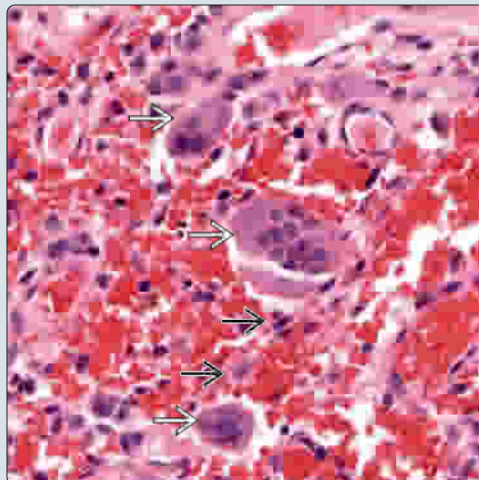


Intact Surface Epithelium in Peripheral Giant Cell Granuloma

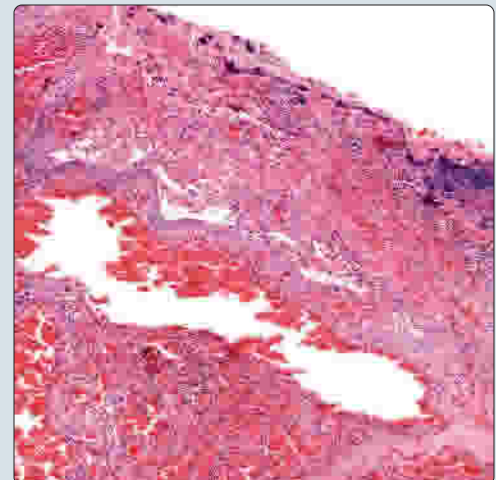


Giant Cells With Blood

(Left) Hematoxylin and eosin shows several multinucleated giant cells  with a background of oval to spindle-shaped stromal cells . Hemorrhage and hemosiderin deposition in the background is characteristic. The mitotic index is generally low. (Right) Hematoxylin and eosin shows an ulcer overlying a vascular stroma with a dense acute and chronic inflammatory infiltrate.



Ulcerated Surface Overlying Stroma



TERMINOLOGY

Abbreviations

- Peripheral giant cell granuloma (PGCG)

Synonyms

- Peripheral giant cell reparative granuloma
- Giant cell epulis

Definitions

- Reactive proliferation of multinucleated giant cells caused by trauma or irritation, exclusive to gingiva or alveolar ridge

ETIOLOGY/PATHOGENESIS

Etiology

- May arise from periodontal ligament or periosteum
- Giant cells show characteristics of osteoclasts
- Consideration for PGCG and peripheral ossifying fibroma hybrid lesion

CLINICAL ISSUES

Epidemiology

- Incidence
 - Common
- Age
 - Wide range; peak: 40-60 years
- Sex
 - Slight female predilection; female > male (1.5:1)

Site

- Exclusive to gingiva or alveolar ridge
- Mandible > maxilla

Presentation

- Red to blue mass; sessile or pedunculated
- Smooth surfaced or may be ulcerated

Treatment

- Surgical approaches
 - Excision down to periosteum, follow for recurrences
- Dental hygiene, with scaling of adjacent teeth

Prognosis

- Recurrences seen in ~ 10%

IMAGING

Radiographic Findings

- Rarely, "cupping" resorption of underlying bone (usually seen intraoperatively)
- Should not have intraosseous component

MACROSCOPIC

General Features

- Nodular mass covered with mucosa
- Rubbery with soft consistency on cut surface

Size

- Usually < 2 cm

MICROSCOPIC

Histologic Features

- Nonencapsulated lesion
- Proliferation of multinucleated giant cells
 - Variable number of nuclei
 - Large vesicular nuclei or small nuclei
- Stroma
 - Plump to ovoid cells
 - Low mitotic index
 - Hemorrhage (interstitial) with hemosiderin pigment deposition
 - Hemosiderin pigment deposition
- Epithelium is frequently ulcerated
 - Fibropurulent membrane
 - Granulation tissue
- Acute and chronic inflammation
- Occasionally dystrophic mineralization or osteoid seen

DIFFERENTIAL DIAGNOSIS

Peripheral Ossifying Fibroma

- Affecting gingiva only
- Cellular stroma with spindled appearance; giant cells; mineralization (bone or calcium)

Pyogenic Granuloma

- Usually lobular arrangement of vessels
- Vascular proliferation with rich inflammatory investment

Fibroma

- Haphazard arrangement of collagen bundles with scant fibroblasts

Parulis of Gingiva

- Distal opening of sinus tract from infected tooth
- Granulation tissue with acute inflammation

Central Giant Cell Lesion

- Central giant cell granuloma
 - Intraosseous, may perforate bone
- Brown tumor of hyperparathyroidism
 - Intraosseous, may perforate bone; parathyroid hormone levels high
- Giant cell tumor
 - Occurs in epiphyses of long tubular bones
- Cherubism
 - Autosomal dominant bony lesion in children; usually affects mandibles bilaterally
 - Usually affects mandibles bilaterally

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KEY FACTS

TERMINOLOGY

- Focal proliferation of fibrous connective tissue in response to local irritation
- Synonyms: Irritation fibroma, traumatic fibroma, focal or localized fibrous hyperplasia

ETIOLOGY/PATHOGENESIS

- Reactive fibrous proliferation due to trauma or irritation
- Trauma: Lip or cheek biting, accidental injury, factitious habits
- Local irritation
 - Accumulation of plaque and calculus
 - Dental restorations with poor contours or margins
 - Orthodontic appliances &/or dentures

CLINICAL ISSUES

- Most common oral cavity "tumor"
- Painful or painless mass
- Affects mucosa or gingiva

- Simple surgical excision is curative

MICROSCOPIC

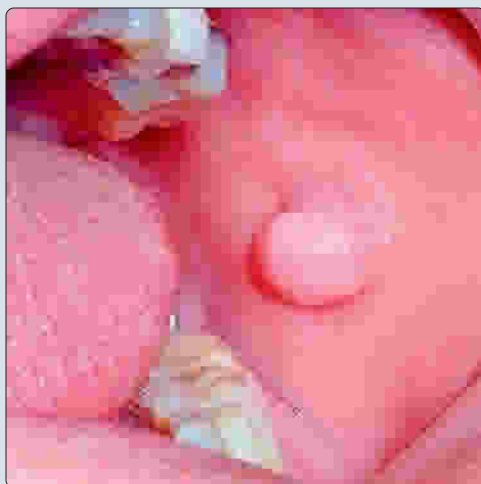
- Usually < 1.5 cm
- Unencapsulated
- Collagen bundles arranged in haphazard fashion
- Covered by stratified squamous epithelium
 - 2° trauma may result in hyperkeratosis or ulcer

TOP DIFFERENTIAL DIAGNOSES

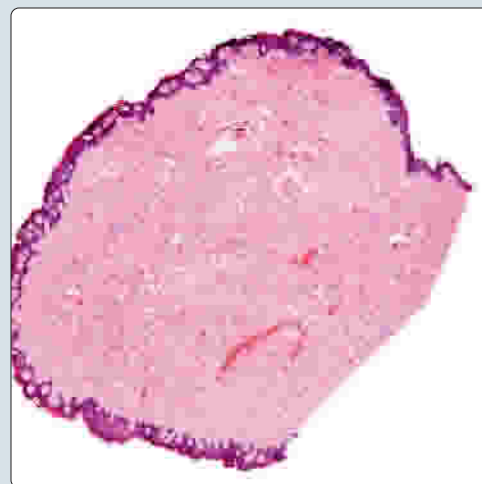
- Peripheral ossifying fibroma
- Pyogenic granuloma
- Peripheral giant cell granuloma
- Granular cell tumor
- Mucocele (retention vs. extravasation)
- Parulis of gingiva
- Mesenchymal tumors
 - Lipoma, hemangioma, neurofibroma, or traumatic neuroma

Buccal Mucosa Fibroma

(Left) Clinical photograph shows a smooth-surfaced nodule on the buccal mucosa. Fibromas like these are often the result of occlusal trauma. **(Right)** Hematoxylin & eosin shows a low-power view of an exophytic nodular mass composed of dense collagen, covered by an intact squamous mucosa.



Polypoid Fibroma

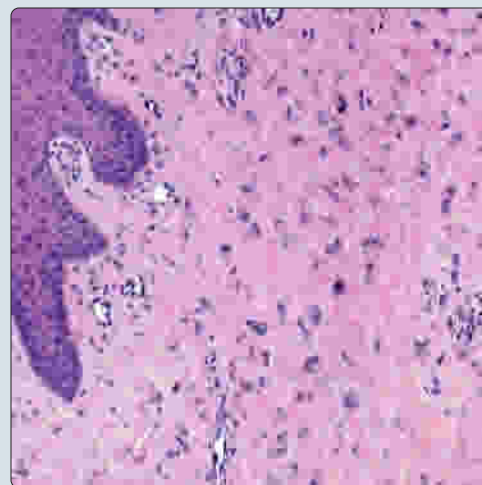


Palate Fibroma

(Left) Clinical photograph shows a smooth-surfaced pink nodule of the hard palate. A squamous papilloma would be in the clinical differential diagnosis. **(Right)** The surface epithelium overlies a cellular fibrotic stroma. There are several enlarged fibroblasts within the collagenized stroma, a finding seen in some irritation fibromas.



Giant Fibroblasts in Stroma



TERMINOLOGY**Synonyms**

- Irritation fibroma
- Traumatic fibroma
- Focal or localized fibrous hyperplasia

Definitions

- Proliferation of fibrous connective tissue in response to local irritation

ETIOLOGY/PATHOGENESIS**Etiology**

- Reactive fibrous proliferation due to trauma or irritation
 - Trauma
 - Lip or cheek biting, accidental injury, factitious habits
 - Local irritation
 - Accumulation of plaque and calculus
 - Dental restorations with poor contours or margins
 - Orthodontic appliances &/or dentures

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Most common oral cavity "tumor"
- Age
 - 4th to 6th decades
- Sex
 - Male > Female (2:1)

Site

- Free mucosal sites
 - Buccal, lip, tongue
- Fixed mucosal sites
 - Gingiva

Presentation

- Papillary or polypoid mass
 - Pain associated with secondary traumatic ulceration

Treatment

- Surgical approaches
 - Simple excision

Prognosis

- Recurrence is rare

MACROSCOPIC**General Features**

- Nodular mass surfaced by mucosa
- May be ulcerated

Size

- Usually < 1.5 cm

MICROSCOPIC**Histologic Features**

- Collagen bundles arranged in haphazard fashion
 - Fibroblasts may have enlarged nuclei: Giant cell fibroma
- Unencapsulated

- Covered by stratified squamous epithelium
 - Epithelium may demonstrate atrophy
 - Secondary trauma may result in hyperkeratosis or ulcer

DIFFERENTIAL DIAGNOSIS**Peripheral Ossifying Fibroma**

- Exclusive to gingiva
- More cellular stroma
- Calcified spicules &/or bone within stroma

Granular Cell Tumor

- Granular eosinophilic cells are set in dense stroma and are S100 protein **positive**

Peripheral Giant Cell Granuloma

- Exclusive to gingiva
- Proliferation of multinucleated giant cells
- Stroma contains plump to ovoid cells with erythrocytes

Pyogenic Granuloma

- Vascular proliferation, usually lobular
- Surface ulceration with rich inflammatory infiltrate

Mucocele (Retention vs. Extravasation)

- Mucin extravasated into stroma
- Adjacent inflamed minor salivary glands

Parulis of Gingiva

- Distal opening of sinus tract from infected tooth
- Granulation tissue with acute inflammation

Mesenchymal Tumors

- Lipoma: Lobular arrangement of fat cells
- Hemangioma: Vascular proliferation
- Neurofibroma: Interlacing bundles of spindle-shaped cells, with wavy nuclei and collagenized-myxoid stroma
- Traumatic neuroma: Haphazard proliferation of mature nerve bundles

Giant Cell Fibroma

- Grossly papillary, with numerous large, stellate fibroblasts

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Peripheral Ossifying Fibroma

KEY FACTS

TERMINOLOGY

- Peripheral ossifying fibroma (POF)
- Reactive proliferation of fibrous tissue with mineralization, exclusive to gingiva

ETIOLOGY/PATHOGENESIS

- May be associated with chronic irritation
- Poorly fitting dentures; orthodontic appliances

CLINICAL ISSUES

- Common lesion
- Wide range, with peak in 2nd decade
- Female > male (2:1)
- Exclusive to gingiva, usually interdental papilla
- Presents as painful or painless mass
- Surgical excision down to periosteum
- Dental hygiene; complete scaling of adjacent teeth to remove local irritants

- Recurrences develop, but complete scaling of adjacent teeth to remove local irritants may help

MACROSCOPIC

- Nodular mass, often ulcerated
- Cut surfaces may reveal gritty mineralized component

MICROSCOPIC

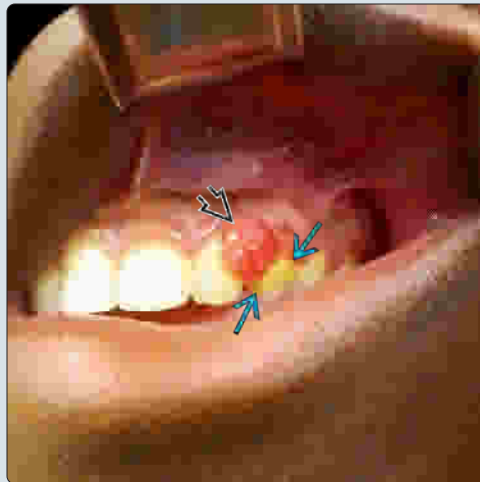
- Cellular fibroblastic stroma
- Mineralized component, showing calcification, bone, or cementum (or combination)
- Surface may be ulcerated

TOP DIFFERENTIAL DIAGNOSES

- Peripheral giant cell granuloma
 - Proliferation of multinucleated giant cells
- Pyogenic granuloma
 - Vascular proliferation, usually lobular
- Fibroma
 - Haphazard bundles of collagen

Clinical Image of Ulcerated POF

(Left) This clinical picture shows a peripheral ossifying fibroma of the maxillary gingiva. It is likely that these lesions are associated with chronic irritation to include plaque and calculus. Removal of the lesion, down to periosteum, and a scaling of adjacent teeth should resolve the condition. (Right) Gross photograph shows an intact squamous mucosa overlying a heavily fibrotic stroma with streaks of ossified material and fibrous connective tissue dissecting between the tissue.

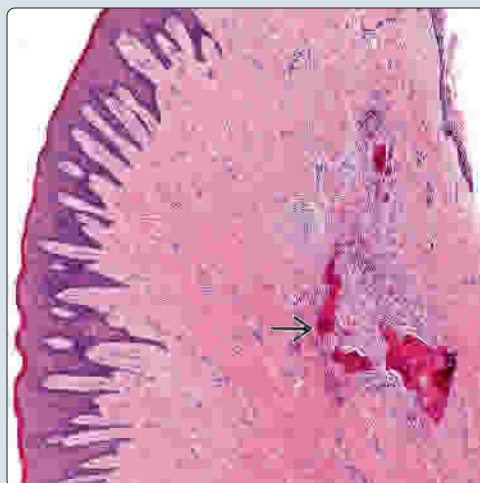


Gross Image With Ossified Material

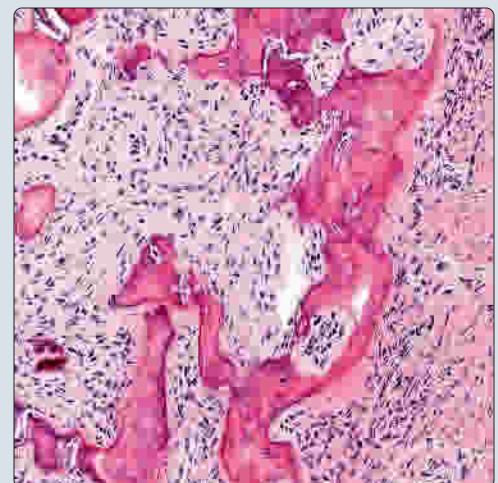


Lesion of the Dental Papilla

(Left) Hematoxylin and eosin shows a nonulcerated fibrous mass with central mineralization. The lesion is composed of only a small fraction of mineralized tissues. Note the overall contours of the specimen represent the interdental papilla, the most common location. (Right) Hematoxylin and eosin shows a cellular fibroblastic proliferation associated with bone.



Mature Bone Found Centrally



TERMINOLOGY

Abbreviations

- Peripheral ossifying fibroma (POF)

Synonyms

- Peripheral fibroma with calcification
- Peripheral odontogenic fibroma
 - Now considered distinct entity

Definitions

- Reactive proliferation of fibrous tissue with mineralization exclusive to gingiva

ETIOLOGY/PATHOGENESIS

Etiology

- May be associated with chronic irritation
 - Poorly fitting dentures; orthodontic appliances
 - Plaque and calculus

Origin

- Cells from periosteum or periodontal ligament
- Immunohistochemistry suggests myofibroblastic proliferation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Common
- Age
 - Wide range with peak in 2nd decade
- Sex
 - Female > male (2:1)

Site

- Exclusive to gingiva, usually interdental papilla
 - More commonly affects maxilla; incisor to canine region

Presentation

- Painful or painless mass
 - Pedunculated or sessile
 - Red or pink; often ulcerated

Treatment

- Dental hygiene; complete scaling of adjacent teeth to remove local irritants
- Surgical excision down to periosteum to reduce recurrence

Prognosis

- Excellent with moderate rate of recurrence
- Recurrences develop when excision is not carried down to periosteum

MACROSCOPIC

General Features

- Nodular mass, usually ulcerated
- Cut surfaces may reveal gritty mineralized component

Size

- Variable, but usually < 2 cm
 - Rare cases of very large lesions have been reported

MICROSCOPIC

Histologic Features

- Cellular fibroblastic stroma
- Mineralized component
 - Rarely absent
 - Woven bone is most commonly identified
 - Trabecular bone less frequently seen
 - Dystrophic calcification
 - Cementum
 - Combination of these may be seen
- Surface may be ulcerated
 - Fibrinopurulent surface deposit
 - Granulation tissue

DIFFERENTIAL DIAGNOSIS

Peripheral Giant Cell Granuloma

- Proliferation of multinucleated giant cells
- Stroma containing plump to ovoid cells

Pyogenic Granuloma

- Vascular proliferation, usually lobular, often with perpendicular vessels
- Reactive endothelial cells with inflammation

Fibroma (Irritation Fibroma)

- Haphazard bundles of collagen
- Lack of calcification or bone

Parulis of Gingiva

- Distal opening of sinus tract from infected tooth
- Granulation tissue with acute inflammation

Giant Cell Fibroma

- Papillary appearance
- Numerous large, stellate fibroblasts

Epulis Fissuratum With Osseous and Chondromatous Metaplasia

- Caused by poorly fitting denture
- Multiple folds of hyperplastic tissue
- Variable chronic inflammatory infiltrate
- May show inflammatory papillary hyperplasia

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KEY FACTS

TERMINOLOGY

- Proliferation of nerves, often in plexiform pattern

ETIOLOGY/PATHOGENESIS

- Multiple endocrine neoplasia (specifically MEN2B)
 - Autosomal dominant, high penetrance, variable expressivity
- Spontaneous mutations in ~ 50%

CLINICAL ISSUES

- Rare solitary cases
- Tongue and lips most frequently
 - Lips: Bilateral commissure is characteristic
 - Less common: Gingiva, palate, buccal mucosa
 - Extraoral sites: Conjunctiva, intestines
- Most cases of multiple lesions are found in patients with MEN2B
- Soft mucosa-colored papules
- No treatment indicated for mucosal neuromas

- Treatment for MEN2B
 - Prophylactic removal of thyroid gland
 - Close follow-up for development of pheochromocytomas

- Solitary lesions: Excellent prognosis



- MEN2B
 - Depends on early diagnosis
 - Specifically determined by associated malignancies

MICROSCOPIC

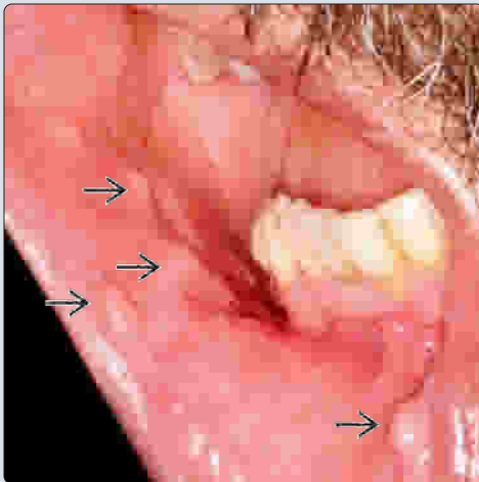
- Nonencapsulated
- Hyperplasia of nerve bundles
- Prominent thickening of perineurium

TOP DIFFERENTIAL DIAGNOSES

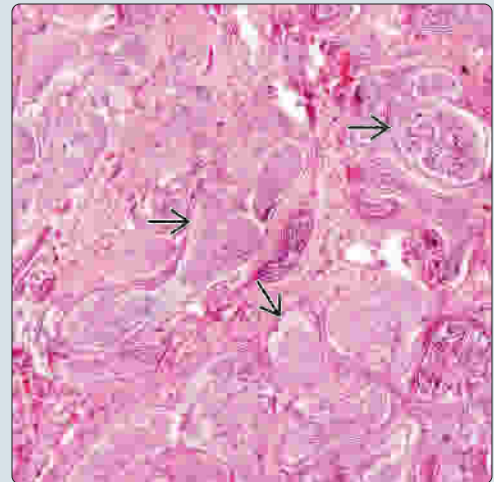
- Neurofibroma
- Traumatic neuroma
- Palisaded encapsulated neuroma
- Schwannoma (neurilemoma)


(Left) Clinical photo shows a patient with multiple endocrine neoplasia (MEN) type 2B. Numerous mucosal neuromas  are common in these patients, frequently the initial presentation of the disease. Early diagnosis of the syndrome is important due to the associated malignancies. **(Right)** Low-power view of a mucosal neuroma shows distinct nerve bundles  haphazardly arranged in a loose fibrovascular connective tissue background.

Oral Photo of Multiple Mucosal Neuromas

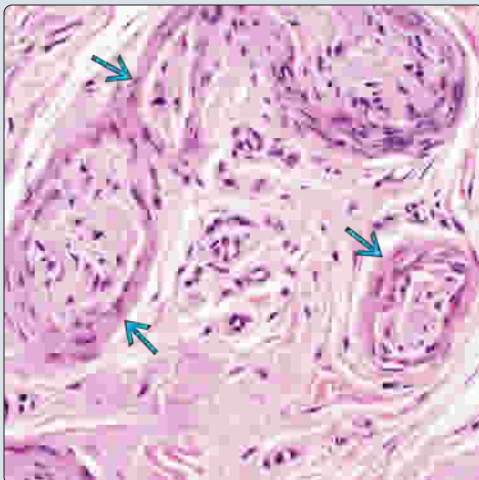


Distinct Nerve Bundles in Neuroma

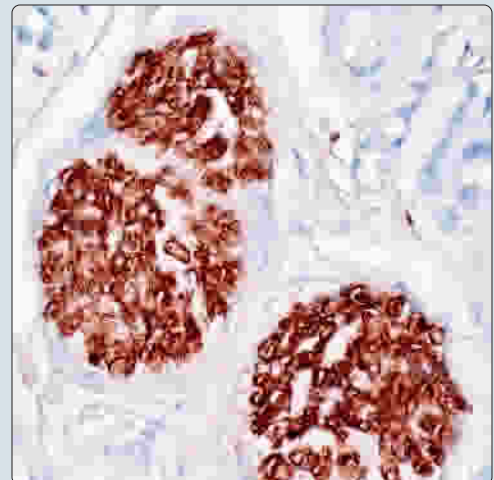


(Left) This medium-power hematoxylin and eosin shows the characteristic thickened perineurium  of a mucosal neuroma. This feature is important and helps differentiate this entity from the more common traumatic neuroma. **(Right)** High-power view shows the intense nuclear and cytoplasmic reactivity with S100 protein immunohistochemistry. While mucosal neuromas are generally an H&E diagnosis, the strong S100 protein reactivity may help differentiate it from a neurofibroma.

Thickened Perineurium



S100 Highlighting Neural Tissue



TERMINOLOGY

Definitions

- Proliferation of nerves, often in plexiform pattern

ETIOLOGY/PATHOGENESIS

Syndrome Association

- Multiple endocrine neoplasia (specifically MEN2B)
 - Germline gain of function mutations of *RET* (chromosome 10q11.2)
 - Autosomal dominant, high penetrance, variable expressivity
 - Spontaneous mutations in ~ 50%
- *PTEN* hamartoma tumor syndrome
 - Cowden or Bannayan-Riley-Ruvalcaba syndromes

CLINICAL ISSUES

Epidemiology

- Incidence
 - Most cases of multiple lesions are found in patients with MEN2B
 - Rare solitary cases
- Age
 - Usually initially identified in childhood
- Sex
 - Equal gender distribution

Site

- Tongue
- Lips: Bilateral commissure is characteristic
- Less common: Gingiva, palate, buccal mucosa
- Extraoral sites: Conjunctiva, intestines

Presentation

- Soft, mucosa-colored papules

Laboratory Tests

- Serologic or genetic evaluation for MEN2B
 - Specifically, calcitonin levels to exclude medullary thyroid carcinoma

Natural History

- MEN2B
 - Mucosal neuromas: Often 1st sign of syndrome
 - Medullary thyroid carcinoma
 - Develops in 2nd or 3rd decade
 - Will occur in 90%
 - Pheochromocytoma (adrenal)
 - Risk increases with age
 - May be bilateral, multifocal or extraadrenal
 - Dysmorphic features
 - Marfanoid, thin face, thickened lips

Treatment

- No treatment indicated for mucosal neuromas
- Treatment for MEN2B
 - Prophylactic removal of thyroid gland
 - Close follow-up for development of pheochromocytomas

Prognosis

- Solitary lesions: Excellent
- MEN2B
 - Depends on early diagnosis
 - Specifically determined by associated malignancies

MACROSCOPIC

General Features

- Mucosa-covered papule

Size

- Small, usually 0.2-0.4 cm

MICROSCOPIC

Histologic Features

- Nonencapsulated, with haphazard distribution
- Hyperplasia of nerve bundles
- Prominent thickening of perineurium surrounding nerve bundles

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** S100 protein, SOX10

DIFFERENTIAL DIAGNOSIS

Neurofibroma

- May blend with surrounding tissue
- Spindle cells with variable collagen
- May be associated with neurofibromatosis

Traumatic Neuroma

- Lacks prominent perineurium
- History of trauma

Palisaded Encapsulated Neuroma

- Encapsulated, at least partially
- Spindle cells

Schwannoma (Neurilemoma)

- Characteristic Antoni A and B
- Verocay bodies
- Hyalinized vessels

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Multiple mucosal neuromas may indicate syndrome association

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KEY FACTS

TERMINOLOGY

- Localized proliferation of benign melanocytes that colonize epithelium

CLINICAL ISSUES

- Most common intraoral locations are palate, gingiva, buccal mucosa, and lip
- Blue nevus most commonly presents intraorally on hard palate
- Like cutaneous counterpart, oral melanocytic nevi have various stages, which correlate with specific microscopic findings
- Up to 15% of intraoral nevi are amelanotic
- Blue nevus 2nd most common intraoral melanocytic nevus
- Any oral pigmentation that cannot be reliably diagnosed based on clinical findings alone should be biopsied
- No reports of malignant transformation of intraoral melanocytic nevi or blue nevi

MICROSCOPIC

- Junctional nevus: Nests of melanocytic nevus cells in basal layer
- Compound nevus: Nests of melanocytic nevus cells in basal cell layer and in lamina propria
- Intramucosal nevus: Nevus cells only present in lamina propria
- Blue nevus: Spindle-shaped melanocytes present deep in lamina propria parallel to epithelium
- Combined nevus with features of both blue nevus and melanocytic nevus have been reported

TOP DIFFERENTIAL DIAGNOSES

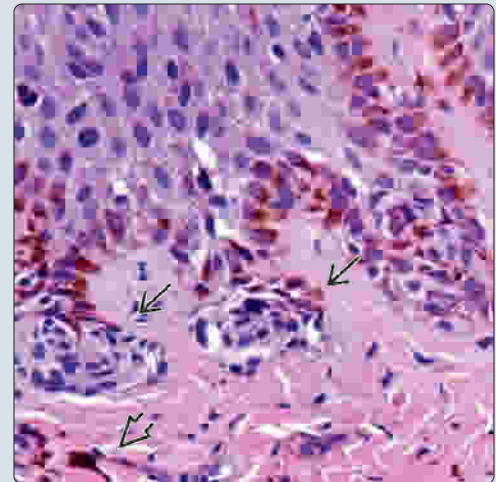
- Melanotic macule/focal melanosis/physiologic pigmentation: Melanin pigment in occasional basal cells
- Melanocanthoma: Acanthotic epithelium with scattered dendritic melanocytes throughout
- Oral melanoma: Acral lentiginous and superficial spreading types

Gingival Junctional Nevus

(Left) Junctional nevus in a 3-year-old child presents as an asymptomatic pigmented lesion of the attached gingiva. This was noted by the mother within the 1st year of life. (Right) High-power photomicrograph of a junctional nevus shows abundant melanin pigment within the basal cells. Single melanocytes and nests of neval cells at the tip of the rete ridges are present. No melanocytic atypia is present. Melanophages can sometimes be present in the superficial lamina propria.



Pigmented Junctional Nevus

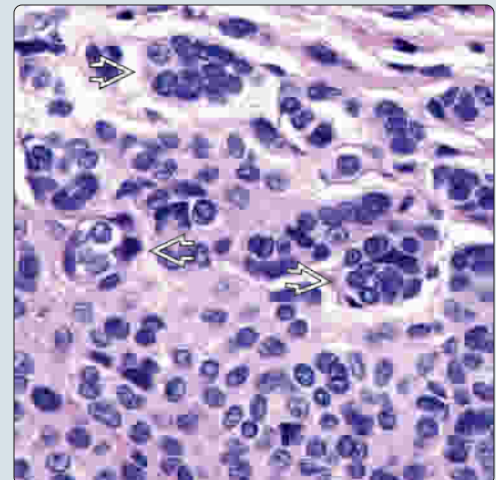


Compound Nevus

(Left) Low-power H&E of a compound nevus of the lip showing uniform nests or thèques of neval cells in the epithelium. Nests of nevus cells are also noted in the superficial lamina propria. Zones of differentiation can be appreciated on this view with larger cells appearing closer to the epithelium, and in the deeper area, the cells appear more spindled. (Right) The superficial zone of a compound nevus shows epithelioid neval cells with abundant cytoplasm. The nevus cells tend to form thèques.



Thèques in Compound Nevus



TERMINOLOGY

Definitions

- Localized proliferation of benign melanocytes that colonize epithelium

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Of neural crest origin, nevus cells migrate to select ectodermal structures during embryogenesis

CLINICAL ISSUES

Epidemiology

- Age
 - Wide range at diagnosis: 3-85 years (mean: 35 years)
- Sex
 - Female > male (1.5:1)
- Ethnicity
 - White patients have more nevi than blacks or Asians

Site

- Most common intraoral locations are palate, gingiva, buccal mucosa, lip
- Blue nevus: Most common on hard palate

Presentation

- Like cutaneous counterpart, oral melanocytic nevi have various stages, which correlate with specific microscopic findings
 - **Junctional nevus**
 - Well demarcated, brown to black macule
 - Generally < 0.6 cm
 - **Compound nevus**
 - Painless tan to brown papule with smooth surface
 - **Intramucosal (intradermal) nevus**
 - Most common intraoral melanocytic nevus
 - Can present as solitary sessile mass and be mistaken for fibroma
 - Usually < 1 cm and up to 15% of intraoral nevi are amelanotic
 - **Blue nevus**
 - 2nd most common intraoral melanocytic nevus
 - Blue coloration due to Tyndall effect
 - Dome-shaped or macule < 1 cm
 - Cellular variant of blue nevus less common, especially in oral cavity

Treatment

- Any oral pigmentation that cannot be reliably diagnosed based on clinical findings alone should be biopsied
 - There should be low threshold for biopsy, particularly if pigment is of recent onset
- Small lesion size makes it amenable to excisional biopsy

Prognosis

- No reports of malignant transformation of intraoral melanocytic nevi or blue nevi
 - This is true, even in patients with multiple nevi

MICROSCOPIC

Histologic Features

- **Junctional nevus**
 - Nests or thèques of melanocytic nevus cells in basal layer
 - Lack of dendritic processes
 - May see variation in nuclear size and shape, but no atypia
 - Mitotic figures rare
- **Compound nevus**
 - Nests of melanocytic nevus cells in basal cell layer
 - Groups of nevus cells begin to "drop off" into superficial lamina propria
 - Pigment in both epithelium and submucosa variable
 - Cellular atypia absent
- **Intramucosal (intradermal) nevus**
 - Thèques of nevus cells are no longer observed in epithelium
 - Nevocytes only present in lamina propria
 - Nevus cells can be variably sized
 - More superficial nevus cells can be larger and epithelioid in appearance, forming nests (thèques)
 - Intracellular melanin frequently seen
 - Nevus cells centrally located are smaller with less cytoplasm and usually lack pigment
 - Lymphocytic appearance
 - Deeper nevus cells are often spindle-shaped similar to Schwann cells
- **Blue nevus**
 - Spindle-shaped melanocytes present deep in lamina propria
 - Cells arranged in parallel fashion to epithelium
 - Abundant melanin pigment with branching dendritic extensions

DIFFERENTIAL DIAGNOSIS

Melanotic Macule/Focal Melanosis/Physiologic Pigmentation

- Melanin pigment in occasional basal cells
- Incontinent melanin &/or melanophages in superficial lamina propria

Melanoacanthoma

- Acanthotic epithelium with scattered dendritic melanocytes throughout

Oral Melanoma

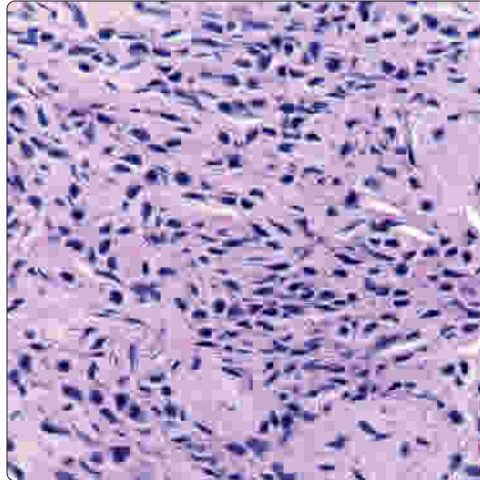
- Acral lentiginous and superficial spreading types
- Atypical melanocytes in basal layer invading superficial epithelium (Pagetoid spread)
- Invasion of melanocytes into lamina propria

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(Left) Nevus cells in the deepest portion of the lamina propria can appear spindled, similar to fibroblasts or Schwann cells. This is a feature of more mature nevi. The nevus cells lack melanin and exhibit a neurotized appearance where the neval cells are palisaded and surrounded by wavy or mature collagen. **(Right)** Pigmented intramucosal (intradermal) nevus of the buccal mucosa is seen with abundant nests of pigmented neval cells in the submucosa. Unlike compound nevus, no neval cells are found in the epithelium.

Neurotized Nevus Cells

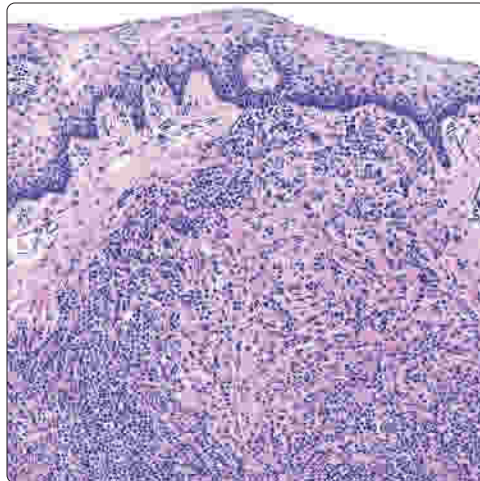


Intramucosal Nevus

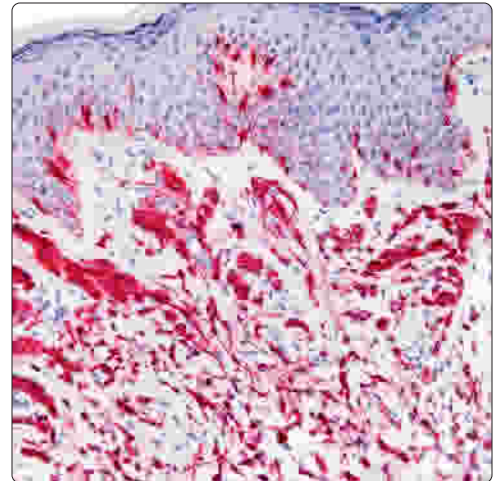


(Left) This intradermal nevus lacks melanin pigment as well as nests of nevus cells. The cells have less cytoplasm and appear more lymphocytic. This more mature type of nevus lacks cytologic atypia and can be confirmed by S100 protein immunohistochemistry. **(Right)** S100 protein with red chromogen highlights the neval cells in the lamina propria of the intramucosal nevus. Melanocytes, including dendritic melanocytes, are also highlighted.

Amelanotic Intramucosal Nevus

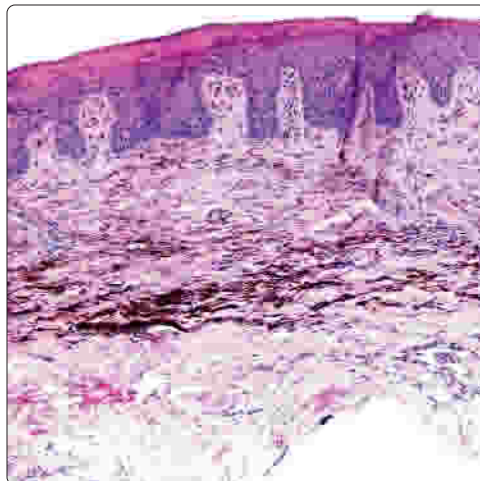


S100 Protein-Positive Intramucosal Nevus

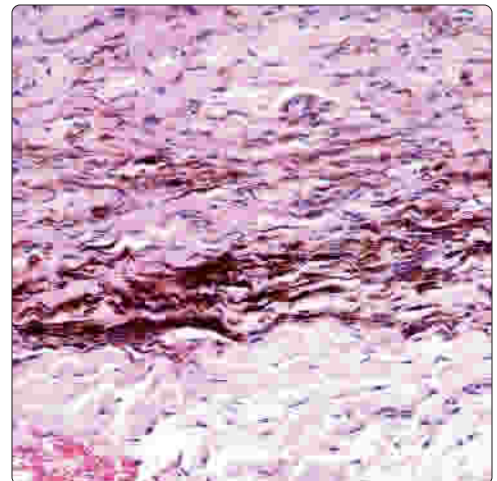


(Left) Blue nevus of the hard palate shows melanin pigment in the deeper lamina propria parallel to the epithelial surface. The blue nevus is typically well delineated from the surrounding tissue. **(Right)** Deeply pigmented, elongated, spindle-shaped melanocytes in the lamina propria are characteristic of a blue nevus. The blue nevus can be associated with an overlying melanocytic nevus, termed a combined nevus.

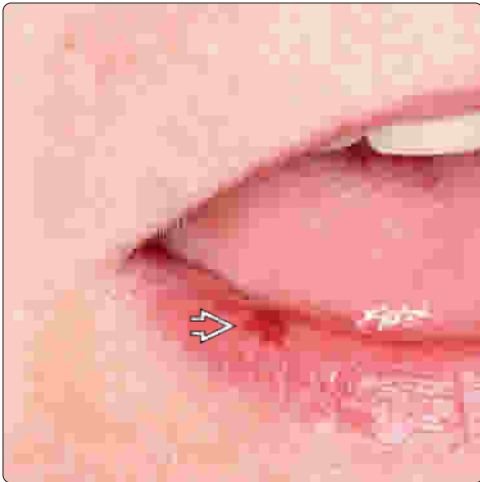
Spindled Cells of Blue Nevus



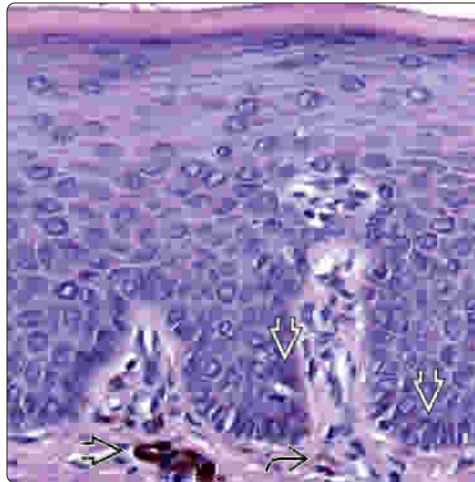
Blue Nevus With Spindled Melanocytes



Lip Melanotic Macule

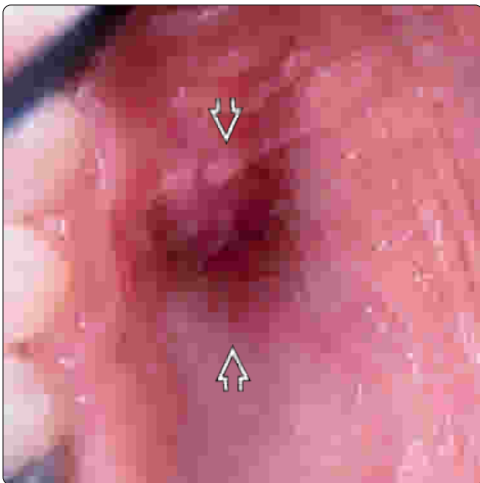


Oral Melanotic Macule



(Left) Oral melanotic macule of the lower lip appears as a uniformly pigmented tan macule. The lower lip is the most common location for melanotic macules, but they can occur anywhere in the oral cavity, including the gingiva, palate, and cheek. (Right) The typical appearance of oral melanotic macules include melanin pigment noted in occasional basal cells and melanophages and incontinent pigment in superficial lamina propria. Increased melanocytes may or may not be seen.

Palatal Melanoacanthoma

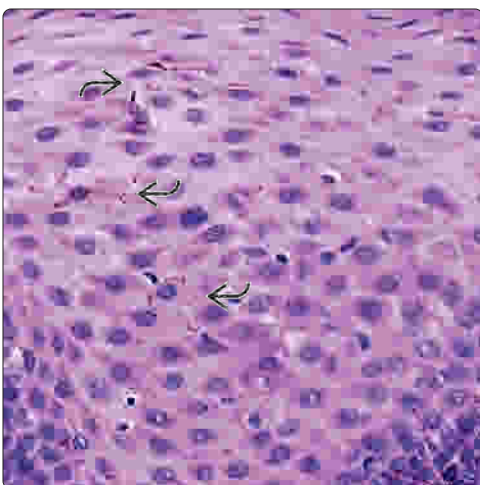


Melanoacanthoma

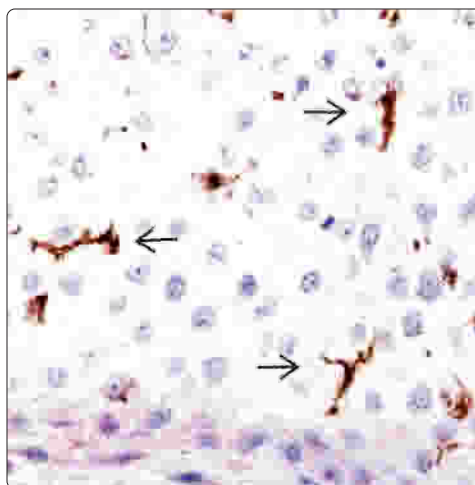


(Left) Clinically, melanoacanthoma can mimic both an intraoral nevus and melanoma. The buccal mucosa is the most common site of occurrence, but the lips, gingiva and palate can be involved. The color can range from light brown to black and can have rapid enlargement causing concern for a malignant process. (Right) Melanoacanthoma from the buccal mucosa demonstrates marked epithelial acanthosis and spongiosis and a chronic inflammatory cell infiltrate with melanin pigment in the superficial lamina propria.

Melanoacanthoma: Dendritic Melanocytes



S100 Highlights Dendritic Melanocytes



(Left) High-power H&E of melanoacanthoma shows dendritic melanocytes within the intercellular spaces of the acanthotic epithelium. (Right) The dendritic cells are present throughout the middle and upper layers of the epithelium. The melanocytes are highlighted by S100 protein immunohistochemistry, which is helpful when the melanocytes are scarce or lightly pigmented. Often the melanocytes are densely pigmented and immunohistochemistry is not required.

KEY FACTS

TERMINOLOGY

- Neoplasm of germ cell origin comprised of mature or immature tissues derived from all 3 germ cell layers
 - Ectoderm
 - Endoderm
 - Mesoderm

ETIOLOGY/PATHOGENESIS

- Arise from pluripotent cells sequestered during embryogenesis

CLINICAL ISSUES

- Most tumors identified prenatally or at birth
 - Ultrasound: Multicystic mass; mixed echogenic signals
- Surgery must be instituted immediately, including ex utero intrapartum treatment procedure
- Worse outcome: Large tumor; intracranial extension
- Rare

- Most are present at birth, may be identified during prenatal screening
- Significant respiratory distress
- Mass protruding from mouth

MICROSCOPIC

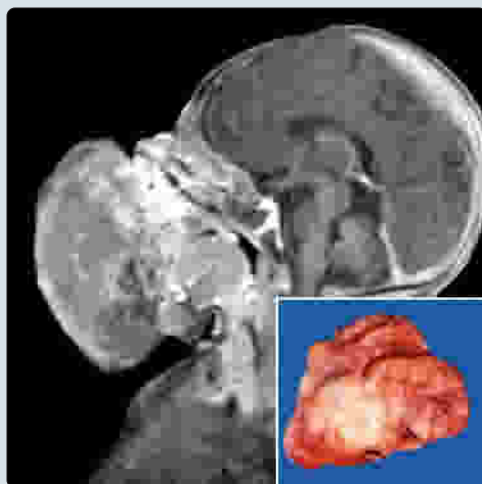
- Most are benign, with any tissue type identified
 - Ectoderm, mesoderm, endoderm derived
- Neural tissue is usually common
 - Primitive neural tissue may indicate malignancy
 - Brain, glial tissue, choroid plexus, pigmented retinal anlage
- Mesenchymal elements (cartilage, bone, muscle, fat)

TOP DIFFERENTIAL DIAGNOSES

- Dermoid cyst
- Encephalocele
- Glial heterotopia

Large Oral Teratoma of Newborn

(Left) Sagittal gadolinium-enhanced scan after delivery shows areas of enhancement within this large solid mass, which involved both the oro- and nasopharynx. The inset shows the resected mass with grumous material. (Right) Gross pathology of the resected mass shows the complex nature of the teratoma. The solid portion had neuroglial elements, fat, smooth muscle, and cartilage.

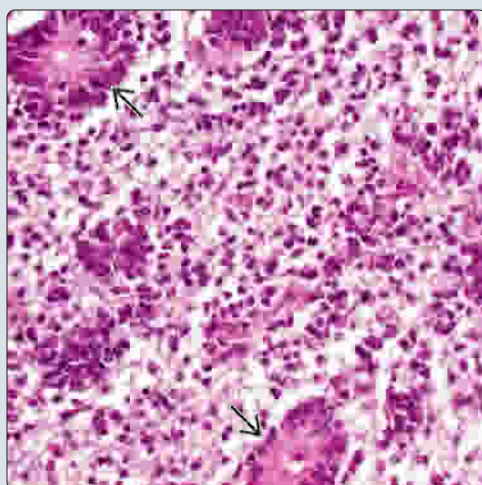


Gross Image of Large Oral Teratoma



Primitive Neural Tissue

(Left) Sometimes primitive neural tissue is present, including rosette formation. Mature neural tissue of all types are common. Primitive neural tissue may, however, indicate malignancy. The specimen should be thoroughly sampled. (Right) This medium-power view shows mature bone with normal hematopoietic bone marrow. Calcification is more common in benign teratomas and can serve as a reassuring finding.



Mature Bone in Teratoma



TERMINOLOGY

Synonyms

- Epignathus: Teratoma that arises in oral cavity

Definitions

- Neoplasm of germ cell origin comprised of mature or immature tissues derived from all 3 germ cell layers: Ectoderm, endoderm, and mesoderm

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Arise from pluripotent cells sequestered during embryogenesis
- Arise from misplaced embryonic germ cells (rests), which develop in new location
- Incomplete division of twins (exceedingly rare)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare: 1 in 4,000 live births have teratoma; 1-2% in H&N
- Age
 - Most are present at birth, may be identified during prenatal screening
- Sex
 - Female > male

Site

- Oropharynx: Palate and tongue

Presentation

- At birth
 - Significant respiratory distress with mass protruding from mouth
- Prenatal
 - Large mass detected by ultrasound
 - Polyhydramnios due to impaired fetal swallowing

Laboratory Tests

- Increased α -fetoprotein concentrations prenatally

Treatment

- Options, risks, complications
 - Respiratory distress, tracheotomy, or oral intubation
 - Unable to feed, requiring nasogastric tube
- Surgical approaches
 - Surgery must be instituted immediately in neonatal/antenatal cases to avoid morbidity or mortality
 - If mass is detected in utero, consider delivering fetus by ex utero intrapartum treatment (EXIT) procedure

Prognosis

- Even though by histology most are benign, bad outcome determined by large tumors or intracranial involvement
- Concurrent germ cell tumors need to be excluded
 - Yolk sac tumor specifically is most significant
- Malignant transformation increases if tumors are not immediately resected
- Recurrences may be seen, but does not imply malignancy

IMAGING

Ultrasonographic Findings

- In utero, at time of birth, or later
- Provide best information and are easiest to obtain
- Most common finding is multicystic mass with mixed echogenic signals

CT Findings

- Inhomogeneous mass, frequently associated with airway compromise

MACROSCOPIC

General Features

- Heterogeneous tissues, firm to soft and cystic
 - Bone, cartilage, hair, teeth are frequently noted
- Gray-tan or yellow-white to translucent cut surface
- Multiloculated, cystic spaces
 - Spaces filled with white-tan creamy material, mucoid glairy material, or dark hemorrhagic fluid

Size

- Up to 15 cm

MICROSCOPIC

Histologic Features

- All 3 primordial layers: Ectoderm, mesoderm, and endoderm
- Wide array of any tissue type
- Variety of epithelial elements (squamous, respiratory, transitional, organs)
- Neural tissue is usually common
 - Brain, glial tissue, choroid plexus, pigmented retinal anlage
 - Primitive neural tissue may indicate malignancy
- Mesenchymal elements (cartilage, bone, muscle, fat)

DIFFERENTIAL DIAGNOSIS

Dermoid Cyst

- More common
- Histology limited to only skin elements
 - Cyst lined by epidermis with skin adnexal structures

Encephalocele

- Displaced neuroglial tissue
- Maintains connection to central nervous system

Glial Heterotopia

- Displaced neuroglial tissue
- No connection to central nervous system

Congenital Rhabdomyosarcoma

- Malignant cells of muscular derivation
 - **Positive:** Desmin, myoglobin, myogenin, actins
- Lacks other tissue types

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Ectomesenchymal Chondromyxoid Tumor

KEY FACTS

TERMINOLOGY

- Benign intraoral tumor presumed origin from undifferentiated (ecto)mesenchymal cell

CLINICAL ISSUES

- Exclusively tongue, anterior dorsal most common location
- Slow-growing, painless mass
- Surgical excision is treatment of choice, excellent prognosis
- Rare, occurs over wide range from 9-78 years old

MICROSCOPIC

- Submucosal unencapsulated but well-delineated or circumscribed nodule(s) separated by fibrous stroma
- Proliferation of small round, oval, spindle or stellate cells
- Chondromyxoid to myxoid stroma, but hyalinized foci may be present
- Absence of glandular &/or myoepithelial components

ANCILLARY TESTS

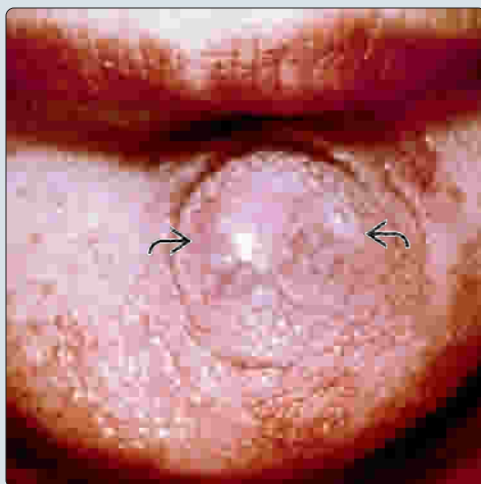
- Glial fibrillary acidic protein **positive** (100% of cases)
- Cytokeratin **positive** (92% of cases)
- S100 protein **positive** (60% of cases)
- Smooth muscle actin **positive** (54% of cases)
- **Negative:** Epithelial membrane antigen, desmin, p63, calponin

TOP DIFFERENTIAL DIAGNOSES

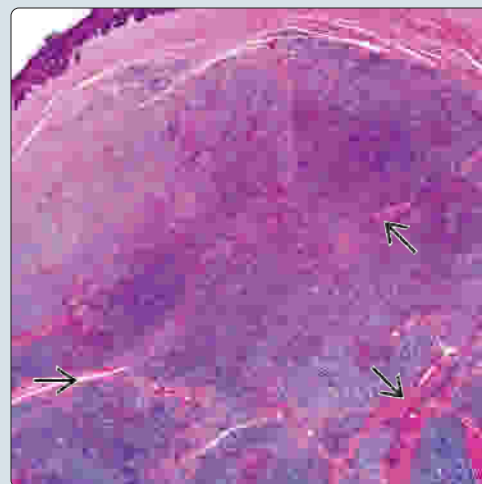
- Pleomorphic adenoma/myoepithelioma
 - Presence of immunohistochemical staining for myoepithelial cells: p63, calponin
- Myxoid neurofibroma
- Nerve sheath myxoma (classic neurothekeoma)
- Ossifying fibromyxoid tumor of soft parts
- Extraskelatal myxoid chondrosarcoma
- Chondroid choristoma
- Focal oral mucinosis
- Mucous retention phenomenon (mucocele)

Tumor of Anterior Dorsal Tongue

(Left) The tumor appears as a submucosal nodule on anterior tongue with intact overlying surface without ulceration. Surgical excision is the treatment of choice with a low recurrence rate. **(Right)** Submucosal circumscribed to well-delineated but unencapsulated hypercellular nodular proliferation with nodular foci separated by fibrous stroma. There is an absence of glandular &/or myoepithelial components. No adjacent minor salivary glands favors this not being a salivary gland neoplasm.

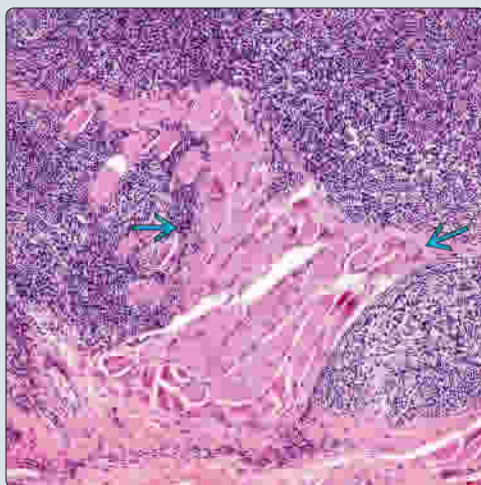


Submucosal, Circumscribed Tumor

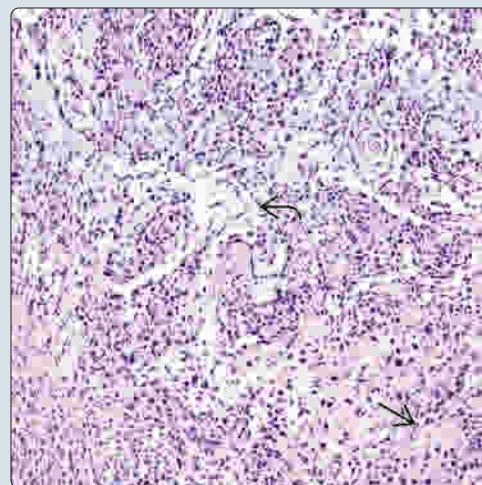


Enveloping Native Muscle

(Left) The tumor frequently will envelop native muscle or nerves. With such a rare tumor, other entities may need to be ruled out with the use of immunohistochemical stains. **(Right)** Cellular proliferation arranged in cords and net-like growth is shown, comprised of cells with small hyperchromatic nuclei and associated chondromyxoid and hyalinized-appearing stroma.



Cellular Proliferation in Net-Like Pattern



TERMINOLOGY

Abbreviations

- Ectomesenchymal chondromyxoid tumor (ECT)

Definitions

- Benign intraoral tumor with presumed origin from undifferentiated (ecto)mesenchymal cell
- Thought to represent myoepithelial tumor type

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare
- Age
 - Wide range (9-78 years); mean: 36.6 years
- Sex
 - Male = female

Site

- Anterior dorsal tongue is most common location

Presentation

- Painless, slow-growing mass

Treatment

- Surgical excision is the treatment of choice

Prognosis

- Excellent

MACROSCOPIC

General Features

- Submucosal circumscribed but not encapsulated nodular mass
 - May have entrapped muscle bundles at periphery
- Cut surface tan-yellow in color with gelatinous appearance

Size

- 0.3-2.0 cm

MICROSCOPIC

Histologic Features

- Submucosal unencapsulated but well-delineated or circumscribed nodule(s) separated by fibrous stroma
- Proliferation of small round, oval, spindle, or stellate cells
 - Uniform-appearing small hyperchromatic nuclei and basophilic to eosinophilic to clear-appearing cytoplasm
 - Cells may be arranged in cords, strands, and so-called net-like sheets
 - Nuclear pleomorphism, multinucleation, and mitotic figures typically not present
 - Cells with atypical pleomorphic hyperchromatic nuclei
 - Absence of atypical mitoses and necrosis
- Chondromyxoid to myxoid stroma but hyalinized stroma may be present
 - Chondroid areas, contain large cells, usually small component
- Swirling formations suggestive of neural differentiation may be present
- Absence of glandular &/or myoepithelial components
- May extend into and entrap soft tissue structures including skeletal muscle and nerve branches

DIFFERENTIAL DIAGNOSIS

Pleomorphic Adenoma/Myoepithelioma

- Salivary gland tumors rarely localized to anterior dorsal tongue
- Presence of identifiable glandular differentiation by light microscopy (PA only), characterized by presence of myoepithelial cells

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Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
GFAP	Positive	Cytoplasmic	Diffuse and strong; 100% of cases
Vimentin	Positive	Cytoplasmic	Diffuse and strong; majority of cases
CK-PAN	Positive	Cytoplasmic	Variable staining (focal to diffuse) in > 90% of cases
S100	Positive	Nuclear & cytoplasmic	Focal moderate to strong in > 60% of cases
SOX10	Positive	Nuclear	Most neoplastic cells
Desmin	Equivocal	Cytoplasmic	Usually negative, with a rare focal staining pattern
Calponin	Negative	Cytoplasmic	Normal staining pattern is cytoplasmic
p63	Negative	Nuclear	Normal staining pattern is nuclear
EMA	Negative	Cytoplasmic	Normal staining pattern is cytoplasmic
Actin-sm	Equivocal	Cytoplasmic	Focal in 30-50% of cases

KEY FACTS

TERMINOLOGY

- **Dysplasia:** Morphologically altered epithelium with increased risk for malignant transformation than in its normal counterpart
- **Carcinoma in situ (CIS):** Dysplasia involving full thickness of epithelium without evidence of invasion into lamina propria
 - Considered to be precancerous and will progress to invasive squamous cell carcinoma if not treated
- **HPV-associated oral intraepithelial neoplasia**
 - Clinical features indistinguishable from non-HPV-associated leukoplakia

MICROSCOPIC

- Both cellular abnormalities and maturation abnormalities are used in grading epithelial dysplasia
- **Hyperplasia:** Increased number of cells leading to acanthosis in basal/parabasal layer
- **Mild dysplasia:** Alteration limited to basal/parabasal layers

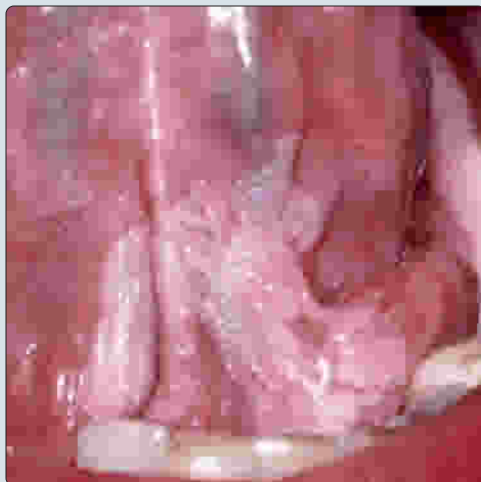
- **Moderate dysplasia:** Alterations from basal layer to midportion of spinous layer
 - If cytologic atypia is marked, then often lesion will be upgraded to severe dysplasia
- **Severe dysplasia:** Dysplasia involving 2/3 to almost complete thickness of epithelium
- **HPV-associated oral intraepithelial neoplasia**
 - Bright eosinophilic parakeratin, less likely orthokeratin, apoptotic and karyorrhectic cells
 - Cytoplasmic and nuclear p16 immunoexpression as continuous linear band
- **Carcinoma in situ:** Dysplastic epithelial cells extend from basal layer to mucosal surface

TOP DIFFERENTIAL DIAGNOSES

- Microinvasive carcinoma
- Verrucous carcinoma
- Proliferative verrucous leukoplakia
- Smokeless tobacco keratoses

Ventral Tongue Leukoplakia

(Left) This is a diffuse area of leukoplakia on the ventral tongue extending to the floor of mouth in a tobacco smoker, which is a high-risk site for development of squamous cell carcinoma (SCC). Early lesions are sometimes reversible with smoking cessation. (Right) Biopsy of the ventral tongue exhibits mild dysplasia with hyperchromatic nuclei present in the basal and parabasal layers but with a normal maturation of the epithelium. These lesions can revert to normal (similar to simple hyperplasia) or progress to a higher grade dysplasia.



Mild Dysplasia

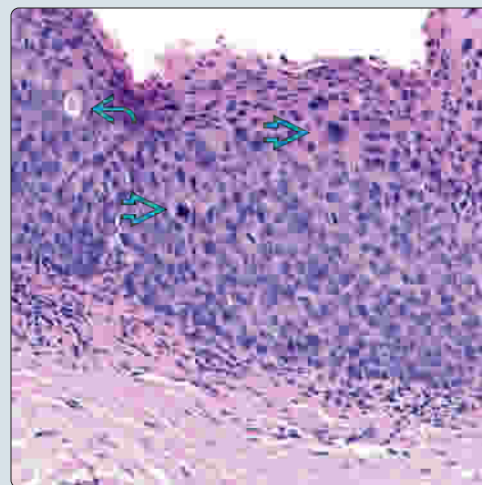


Erythroleukoplakia of Soft Palate

(Left) Erythroleukoplakia of the soft palate shows irregular areas of thickened homogeneous white plaques with speckled areas of erythema. Biopsy selection is important and should include the erythematous component. (Right) Carcinoma in situ of the soft palate exhibits full thickness cellular abnormalities, including marked pleomorphism, atypical mitotic figures, and dyskeratosis contained by an intact basement membrane.



Carcinoma In Situ



TERMINOLOGY

Synonyms

- Dysplasia (mild, moderate, severe)
- Squamous intraepithelial lesion (SIL) or neoplasia (SIN)
- Leukoplakia
- Erythroplakia

Definitions

- **Dysplasia**
 - Morphologically altered epithelium with increased risk for malignant transformation compared with its normal counterpart
- **Carcinoma in situ (CIS)**
 - Dysplasia involving full thickness of epithelium without evidence of invasion into lamina propria
 - Considered to be precancerous and will progress to invasive squamous cell carcinoma (SCC) if not treated
- **Oral leukoplakia**
 - Clinical term of exclusion and does not imply that microscopic tissue alteration is present
 - White patch that cannot be given another specific diagnostic name
 - Often divided into 2 subtypes
 - Homogeneous leukoplakia: Uniformly white
 - Nonhomogeneous or erythroleukoplakia: Has erythematous component
- **Oral erythroplakia (erythroplasia)**
 - Red patch or plaque that cannot be given another specific diagnostic name
- **HPV-associated oral intraepithelial neoplasia**
 - Associated with high-risk HPV subtypes
 - Clinical features indistinguishable from non-HPV associated leukoplakia

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Strong association with tobacco smoking
 - 70-90% of oral leukoplakias found in smokers
 - Heavy smokers have more numerous and larger lesions than light smokers
- Ultraviolet radiation
 - Leukoplakia of lower lip vermillion

Infectious Agents

- Candidal organisms
 - Often seen in association with dysplasia
 - Unknown whether organism is causative or secondarily infects dysplastic mucosa
- Human papillomavirus (HPV)
 - Not commonly seen in oral leukoplakia
 - Subset of oral dysplasias are associated with high-risk HPV and p16
 - Uncertain whether HPV infection is prognostic marker for malignant transformation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Exact incidence of oral dysplasia unknown

- Prevalence of oral leukoplakia in Western countries ~ 2%
- Dysplastic changes found in < 25% of leukoplakia biopsies
- Erythroplakia significantly less common but > 90% of cases exhibit dysplasia, CIS, or invasive SCC

- Age
 - Usually > 40 years, increases rapidly with age
- Sex
 - Male > female (2.3:1)

Site

- Can occur anywhere
 - Most common sites with highest risk of malignant transformation: Lateral and ventral tongue, floor of mouth, and lower lip

Presentation

- White, red, or red and white patch

Natural History

- Risk of malignant transformation
 - Mild and moderate dysplasia: May be reversible
 - Reactive changes can be induced by candidiasis, ulcers, and mechanical irritation
 - Some reports of mild dysplasia progressing to SCC
 - Malignant transformation rates of leukoplakia (without dysplasia) range from 1-4%
 - Most erythroplasia will undergo malignant transformation if not excised

Treatment

- Options, risks, complications
 - Cessation of possible etiologies (tobacco smoking) may reverse clinical leukoplakia and mild to moderate dysplasia
- Surgical approaches
 - Excisional biopsy or laser ablation of abnormal area particularly in severe dysplasia or CIS (high-grade dysplasia)

Prognosis

- No reliable marker to predict progression to SCC
- Recurrence rates after treatment: Up to 30%
 - No data on recurrence rate after erythroplakia excision
- Risk factors for malignant transformation of leukoplakia include
 - Long duration, erythroplasia, tongue or floor of mouth location, female, presence in nonsmokers

MACROSCOPIC

General Features

- **Leukoplakia**
 - Thin white, gray or translucent plaque may be earliest presentation
 - Progresses to more thickened, white keratotic plaque that may have corrugated appearance
 - Nodular appearance with surface irregularities of verruciform appearance
 - Can develop scattered areas of erythroplakia representing nonkeratinizing epithelium (speckled leukoplakia/erythroleukoplakia)

- **Erythroplakia**
 - Well-demarcated red plaque with soft, velvety texture

MICROSCOPIC

Histologic Features

- Cellular **and** maturation abnormalities are used in grading epithelial dysplasia
 - **Maturation abnormalities**
 - Drop-shaped rete ridges
 - Loss of polarity of basal cells
 - Loss of maturation with increased cellularity in spinous layer
 - Dysplastic process begins in basal/parabasal layer
 - **Cellular abnormalities**
 - Nuclear pleomorphism and hyperchromasia
 - Enlarged nucleoli (may be noted in reactive processes)
 - Increased nuclear to cytoplasmic ratio
 - Increased mitotic activity
 - Abnormal mitotic figures
 - Dyskeratosis
- **Grading dysplasia**
 - **Hyperplasia**
 - Increased number of cells leading to acanthosis in basal/parabasal layer
 - Some leukoplakias exhibit epithelial atrophy
 - No cellular atypia
 - Normal maturation
 - May be either ortho- or parakeratinized or both
 - **Mild dysplasia**
 - Alteration limited to basal/parabasal layers
 - Acanthosis
 - May have occasional lymphocytes
 - **Moderate dysplasia**
 - Alterations from basal layer to midportion of spinous layer
 - Bulbous rete ridges
 - Moderate number of lymphocytes are often seen
 - If cytologic atypia is marked, then often lesion will be upgraded to severe dysplasia
 - **Severe dysplasia**
 - Dysplasia involving 2/3 to almost complete thickness of epithelium
 - Epithelial atrophy
 - May have both keratinized and nonkeratinized areas
 - Dysplasia can be seen extending into underlying salivary gland ducts
 - Moderate to marked lymphocyte infiltrate in stroma subjacent to epithelium
 - Inflammatory cell exocytosis may be seen
 - Some experts feel severe dysplasia is synonymous with CIS
- **HPV-associated oral intraepithelial neoplasia**
 - Bright eosinophilic parakeratin, less likely orthokeratin
 - Full-thickness dysplasia
 - Readily identifiable apoptotic and karyorrhectic cells
 - Koilocytes present in small numbers
 - Cytoplasmic and nuclear p16 immunoexpression as continuous linear band
 - Nuclear positivity for high-risk HPV by in situ hybridization
- **Carcinoma in situ**
 - Dysplastic epithelial cells extend from basal layer to mucosal surface
 - Basement membrane remains intact
 - Lesion is usually nonkeratinized
 - Keratin pearl formation unusual in CIS and may suggest invasive SCC in adjacent tissue
 - Dysplasia may extend into underlying salivary gland ducts

DIFFERENTIAL DIAGNOSIS

Reactive Atypia

- Can be seen in epithelium adjacent to ulcers, including aphthous ulcers, herpetic lesion, and traumatic ulcers
- Neutrophilic infiltrate in superficial lamina propria may indicate presence of fungi, in particular *Candida* species
 - Special stains (periodic acid-Schiff) will highlight hyphae &/or spores on epithelial surface of superficial keratin

Microinvasive Carcinoma

- Biopsies of severe dysplasia or CIS should have multiple levels evaluated for definitive evidence of invasion into lamina propria
- Careful evaluation of epithelial/lamina propria interface needed
- If biopsy of severe dysplasia CIS represents small sample of larger lesion, additional sampling or complete removal is recommended

Verrucous Carcinoma

- Verrucous leukoplakia share many histologic features with verrucous carcinoma and may be difficult to distinguish microscopically
- Verrucous carcinomas present as large, exophytic masses

Proliferative Verrucous Leukoplakia

- Unique form of leukoplakia characterized by multiple flat keratoses that eventually develop verrucal or exophytic appearance

Smokeless Tobacco Keratoses

- Area of keratoses corresponding to where smokeless tobacco is placed (usually buccal vestibule)

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Lateral Tongue Leukoplakia

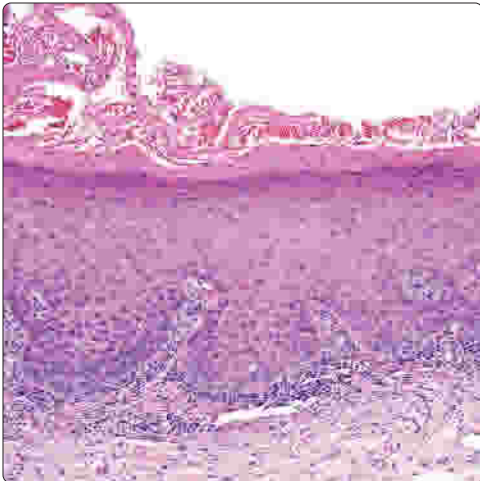


Ortho- and Parakeratosis in Leukoplakia

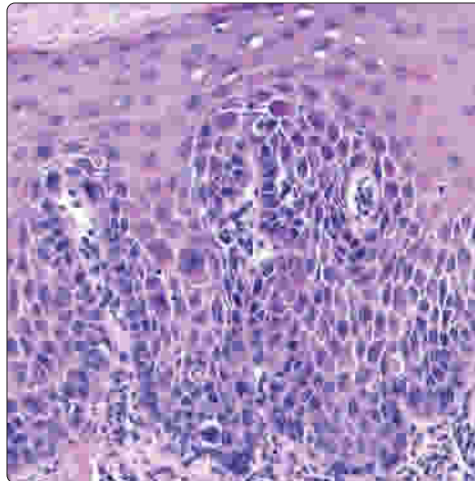


(Left) A diffuse area of leukoplakia extending from the lateral/ventral tongue to the floor of mouth is seen. The homogeneous leukoplakia is thick with fissuring present. Biopsy did not show any dysplasia, but this is a high-risk location for progression to SCC. (Right) Biopsy of clinical leukoplakia shows areas of both parakeratosis and orthokeratosis without dysplasia. Although parakeratin is most frequently observed, the presence of orthokeratin does not have any prognostic implications.

Epithelial Rete Ridge Budding

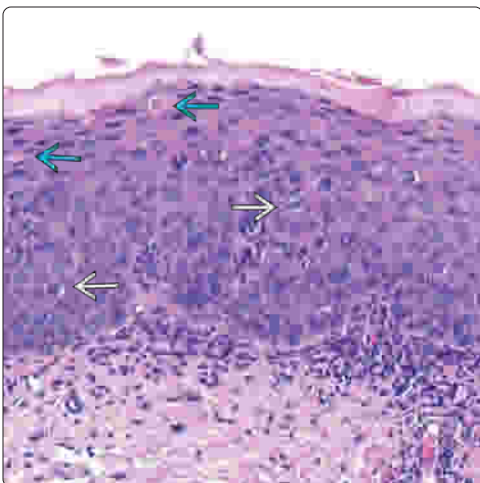


Moderate Dysplasia



(Left) Drop-shaped, or budding of the rete ridges, is a histomorphologic feature that can be seen even without any cytologic abnormalities. This feature, especially in combination with epithelial atrophy, and location on the tongue or floor of the mouth should upstage the grading. (Right) Biopsy of moderate dysplasia shows elongated rete with marked acanthosis, nuclear pleomorphism, and mitoses extending to the middle 1/3 of the epithelium. Potentially reversible, complete removal is warranted, if possible.

High-Grade Dysplasia



Abrupt Transition to Invasive Carcinoma



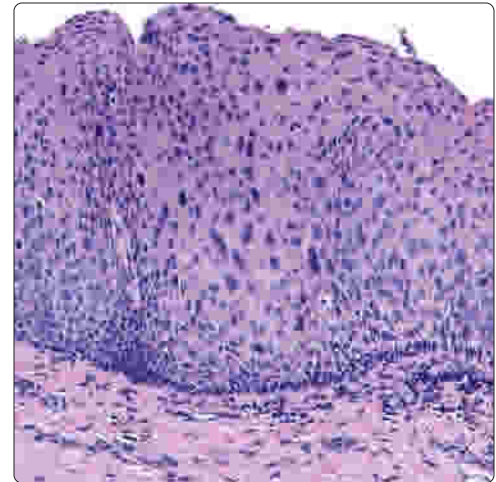
(Left) Keratinizing dysplasia involving the entire thickness of the surface epithelium is seen. Numerous mitotic figures and dyskeratotic cells are evident, even in the parakeratin. Grading keratinized severe dysplasia/CIS is less reproducible than nonkeratinized dysplasia. (Right) Invasive squamous cell carcinoma arising adjacent to epithelium exhibits little to no dysplasia. Although uncommon, malignant transformation can occur in nondysplastic oral leukoplakia.

Erythroplakia of Soft Palate

(Left) Erythroplakia of the soft palate presents as a well-demarcated lesion with a velvety surface. Unlike oral leukoplakia in which most biopsies show no dysplasia, erythroplakia usually shows severe dysplasia, CIS, or SCC when biopsied. (Right) Biopsy of an area of erythroplakia shows a full-thickness abnormal maturation with marked cellular pleomorphism but without violation of the basement membrane.

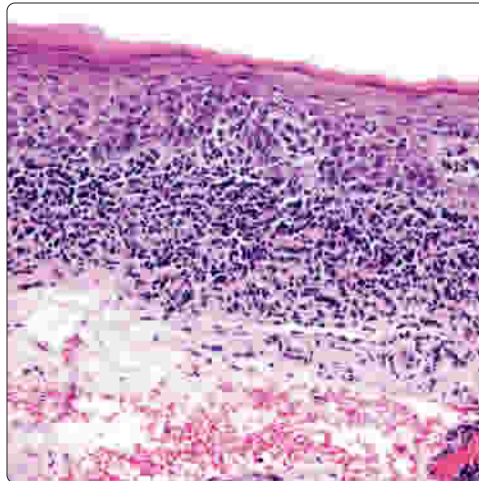


Nonkeratinizing Carcinoma In Situ

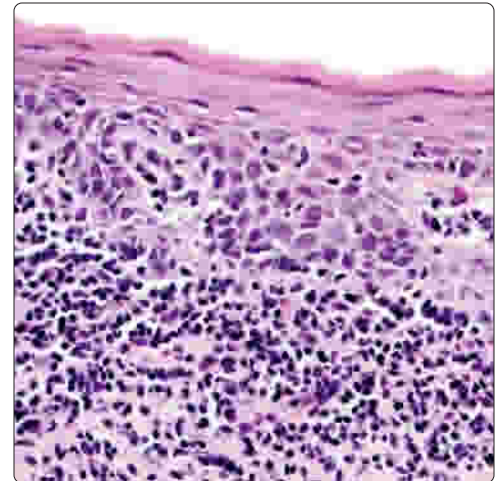


Dysplasia Mimicking Lichen Planus

(Left) Low-power photomicrograph of a white lesion on the ventral tongue exhibits epithelial atrophy with irregularly shaped rete. A prominent inflammatory cell infiltrate is subjacent to the basal cells, imparting a "lichenoid" appearance. (Right) Higher power view shows features of moderate dysplasia, including hyperchromatic and pleomorphic nuclei extending to the midpoint of the epithelium. This should not be mistaken for lichen planus.

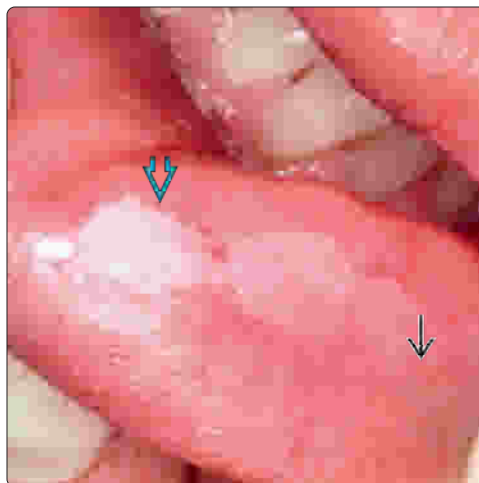


Dysplasia With Lichenoid Features



Long-Term Sun Exposure: Actinic Changes

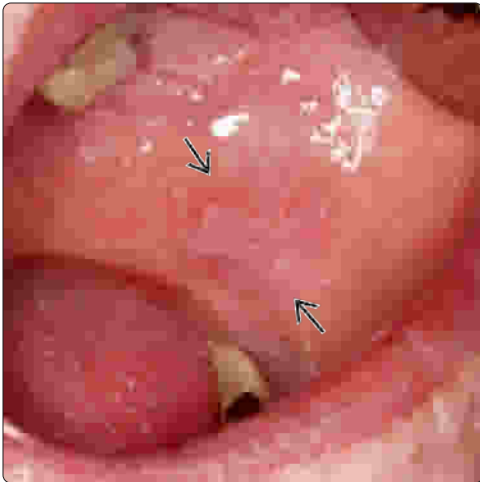
(Left) Actinic cheilosis is a common precancerous condition associated with ultraviolet radiation. Blurring of the vermillion border and cutaneous portion is seen along with thickened keratotic plaques. (Right) Biopsy of actinic cheilosis is characterized by atrophic epithelium with marked parakeratosis. The epithelium exhibits dysplastic changes that extend into the hair follicle. Amorphous, basophilic alteration of the connective tissue (solar elastosis) is seen.



Solar Elastosis With Actinic Cheilosis



HPV-Associated Oral Intraepithelial Dysplasia

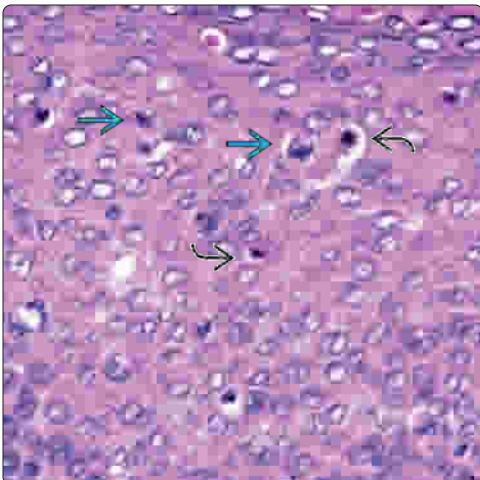


Eosinophilic Parakeratosis and Epithelial Hyperplasia



(Left) A mixed red and white rough lesion on the buccal mucosa [1] of a 65-year-old female with a history of cigarette smoking is seen. The area was sensitive to spicy foods and the patient noticed the rough area with her tongue. (Right) Low-power photomicrograph of a biopsy from the buccal mucosa demonstrated marked epithelial hyperplasia with eosinophilic compact parakeratosis. Even on low-power, maturation disarray is evident, as is scattered large atypical cells [2].

Marked Karyorrhexis and Apoptosis

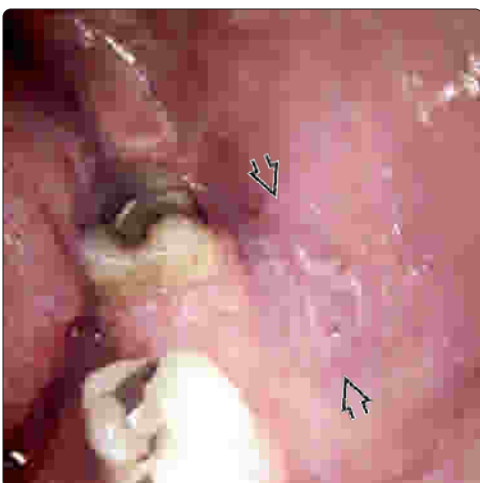


Full-Thickness p16(+) in HPV-Associated Oral Intraepithelial Neoplasia

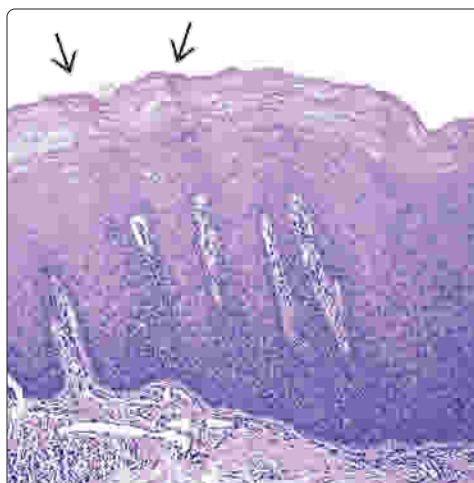


(Left) Characteristic of this lesion, throughout the epithelium mark karyorrhexis [3] is identified in HPV-associated oral intraepithelial dysplasia, as is apoptosis [4]. Scattered koilocytes may be identified, but are usually in small numbers. (Right) Strong and diffuse nuclear and cytoplasmic positivity for p16 in HPV-associated oral intraepithelial neoplasia is shown. In situ hybridization studies for high-risk HPV are also positive. Due to few reported cases, the biologic behavior of these lesions is not well known.

Smokeless Tobacco Pouch Keratosis



Chevron Keratinization in Smokeless Tobacco Keratosis



(Left) A white leathery plaque in the mandibular vestibule in the area of smokeless tobacco placement [5] is seen. Most of the lesions are reversible within a few weeks after cessation of the tobacco habit. (Right) Most smokeless tobacco keratoses demonstrate epithelial acanthosis, hyperparakeratosis but no dysplasia. Parakeratin "chevrons" [6] may be seen as pointed projections. Epithelial dysplasia is unusual in smokeless tobacco keratosis and when present is usually mild dysplasia.

Proliferative Verrucous Leukoplakia

KEY FACTS

TERMINOLOGY

- Rare and unique form of oral premalignancy requiring clinical and pathologic correlation

ETIOLOGY/PATHOGENESIS

- No link with smokeless and smoked tobacco, alcohol use, or areca nut
- No link with viruses including Epstein-Barr virus (EBV) and human papillomavirus

CLINICAL ISSUES

- Predilection for women: Female > > male (4:1)
- Occurs in older patients (generally > 60 years of age)
- Unrelenting progressive disease with high recurrence rate and 5-year survival rates

MICROSCOPIC

- Marked keratosis with verrucoid or church spire pattern
- Epithelial hyperplasia with elongated slightly bulbous rete

- Band-like subepithelial chronic inflammatory cells mimicking lichen planus

TOP DIFFERENTIAL DIAGNOSES

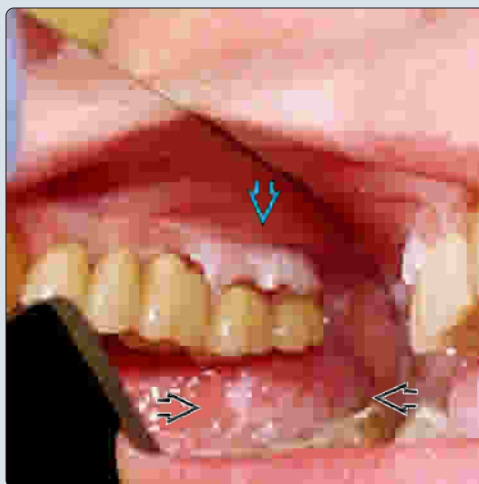
- **Conventional leukoplakia:** Lateral/ventral tongue and floor of mouth are most common sites
- **Lichen planus:** Bilateral and symmetrical
- **Oral hairy leukoplakia:** Associated with EBV

DIAGNOSTIC CHECKLIST

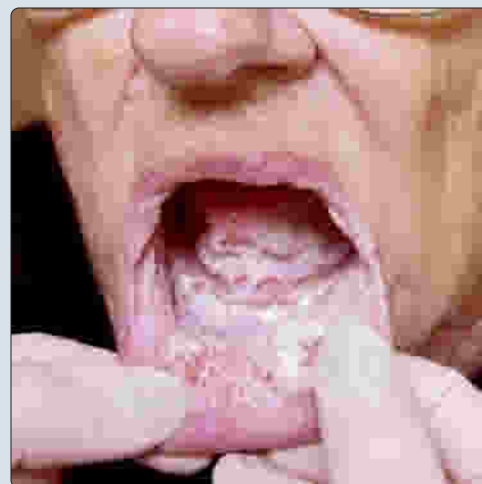
- Proliferative verrucous leukoplakia (PVL) can exhibit wide range of histologies: Normal keratoses to verrucoid keratoses to atypical epithelial hyperplasia to dysplasia to verrucous carcinoma or conventional squamous cell carcinoma
- Often diagnosis made in retrospect aided by high degree of suspicion
- Diagnosis requires good communication between pathologist and clinician

Clinical Mirror Photo of Proliferative Verrucous Leukoplakia

(Left) Photograph of PVL in a 70-year-old woman with no history of smoking or alcohol abuse is shown. PVL has a predilection for the gingiva, which is a common site for malignant transformation unlike more typical oral leukoplakia. Extensive, white, thickened, and fissured areas are seen on the gingiva [A] and tongue [B]. (Right) Elderly woman with no history of smoking or alcohol use presents with diffuse PVL involving most of the oral cavity is shown. Unlike Candidiasis, these plaques do not wipe off.



Diffuse Oral Involvement by Proliferative Verrucous Leukoplakia

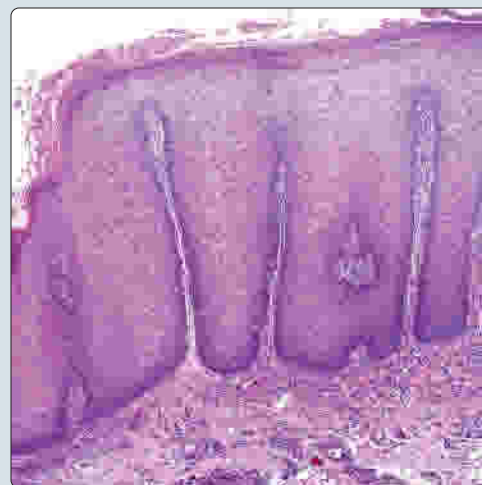


Atypical Verrucous Epithelial Hyperplasia

(Left) Photomicrograph shows atypical verrucous epithelial hyperplasia in a patient with PVL. Marked hyperkeratosis corresponds to the clinical features of thickened and fissured mucosa. The rete are bulbous, similar to verrucous carcinoma. (Right) Low-power image shows atypical epithelial hyperplasia in a patient with PVL. Surface keratinization is not abundant. Marked acanthosis is seen with elongated rete. No significant dysplastic findings are seen, but the overall architecture is worrisome for progression to cancer.



Atypical Epithelial Hyperplasia



TERMINOLOGY

Abbreviations

- Proliferative verrucous leukoplakia (PVL)

Definitions

- Rare and unique form of oral premalignancy requiring clinical and pathologic correlation

ETIOLOGY/PATHOGENESIS

To Date, No Known Risk Factors

- No link with smokeless and smoked tobacco, alcohol use or areca nut
- No link with viruses: Epstein-Barr virus (EBV), human papillomavirus (HPV)

CLINICAL ISSUES

Epidemiology

- Female >> male (4:1)
- Occurs in older patients, generally > 60 years of age

Presentation

- Early lesion
 - Generally asymptomatic single or multiple hyperkeratotic thickened plaque(s)
 - Lesions often involve gingiva or alveolar ridge, palate and buccal mucosa
 - Can have verrucoid appearance
- Progression of PVL
 - Larger areas involved
 - Verrucoid appearance more obvious
 - May see erythema &/or ulceration
 - Candidal overgrowth
- Progression to cancer
 - Both verrucous carcinoma and conventional squamous cell carcinoma may occur
 - Site of cancer development often is gingiva/alveolar mucosa, palate and buccal mucosa

Treatment

- No curative treatment exists
 - Conservative surgical excision usually fails as disease has wide field effect
 - Other therapies including radiation, cryotherapy, laser ablation, and photodynamic therapy have been tried without efficacy
- Close clinical surveillance to detect early squamous cell cancer with appropriate local excision considered most judicious course

Prognosis

- Unrelenting progressive disease with high recurrence rate and 5-year survival rates
- Low incidence of bone invasion and cervical lymph node metastasis

MICROSCOPIC

Histologic Features

- **PVL can exhibit wide range of histologies from normal keratoses to verrucous carcinoma or conventional squamous cell carcinoma**
 - Subtle pathology changes associated with PVL will be discussed
 - Features of SCC are discussed in detail elsewhere
- Marked keratosis with verrucoid or church spire pattern
- Epithelial hyperplasia with elongated slightly bulbous rete
- Band-like subepithelial chronic inflammatory cells mimicking lichen planus
- Candidal overgrowth often present in keratin

DIFFERENTIAL DIAGNOSIS

Conventional Leukoplakia

- Usually single, flat homogenous white lesion
- Lateral/ventral tongue and floor of mouth are most common sites

Lichen Planus

- Bilateral and symmetrical
- No epithelial dysplasia or verrucous hyperkeratosis

Oral Hairy Leukoplakia

- Associated with EBV; immunosuppression (AIDS, organ transplant)
- Tongue is most common location

Oral Condyloma

- Usually single focus, associated with HPV

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Diagnosis often made in retrospect with high degree of suspicion
- Requires good pathologist and clinician communication

Pathologic Interpretation Pearls

- PVL can exhibit wide range of histologies: Normal keratoses to verrucoid keratoses to atypical epithelial hyperplasia to dysplasia to verrucous carcinoma or conventional squamous cell carcinoma
- Marked verrucous keratosis not commonly seen in conventional oral leukoplakia

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KEY FACTS

ETIOLOGY/PATHOGENESIS

- Tobacco use, alcohol consumption, UV radiation, immunosuppression
- Betel quid (Paan): Combination of areca palm nuts, betel leaf, slaked lime, ± tobacco

CLINICAL ISSUES

- Accounts for > 90% of all oral cavity malignancies
- Most common in men in 6th and 7th decades
- Tongue (lateral and ventral) accounts for > 50% of cases
- Lip (> 90% found on lower lip) due to UV exposure
- Treatment includes surgery &/or radiation ± chemotherapy
- Disease-free survival and overall survival correlates with TNM staging
 - Resection margins, perineural and lymph-vascular invasion
 - Lymph node metastases and extracapsular spread
- ~ 10% increased risk of 2nd aerodigestive malignancy

MICROSCOPIC

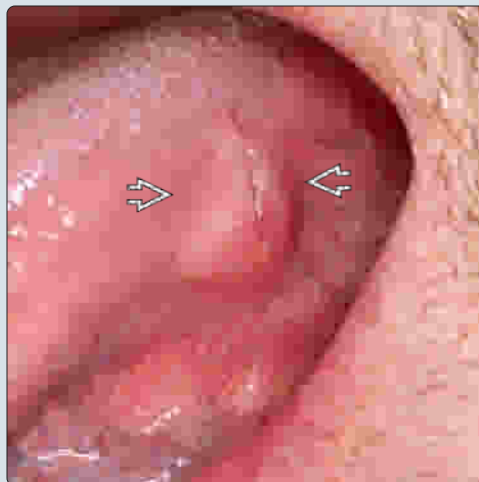
- Majority of oral cavity squamous cell carcinomas (SCCs) are conventional keratinizing type
- Histologic grade includes well-, moderately, and poorly differentiated SCC
- Adjacent areas of dysplasia or CIS can be identified, but invasion can be seen without surface atypia
- Tumor spread influenced by anatomic location
- Variants of keratinizing SCC may be found
 - **Verrucous carcinoma**: > 75% found in oral cavity
 - Marked epithelial hyperplasia with broad elongated rete with pushing border
 - **Carcinoma cuniculatum**: Proliferation of epithelium with endophytic growth pattern with deeply penetrating crypts filled with keratin

TOP DIFFERENTIAL DIAGNOSES

- Pseudoepitheliomatous hyperplasia, necrotizing sialometaplasia, radiation changes

Lateral Tongue Squamous Cell Carcinoma

(Left) A 40-year-old male with a T1 squamous cell carcinoma (SCC) arising on the posterior lateral border of the tongue presented as an exophytic mass with a central ulcer. On palpation, the lesion was firm and indurated. The patient had a positive lymph node on examination of the neck dissection. (Right) Although much of the surface epithelium does not exhibit high-grade dysplastic changes in the central area, widely dispersed small tumor islands are present along with an isolated tumor island away from the main invasive front.

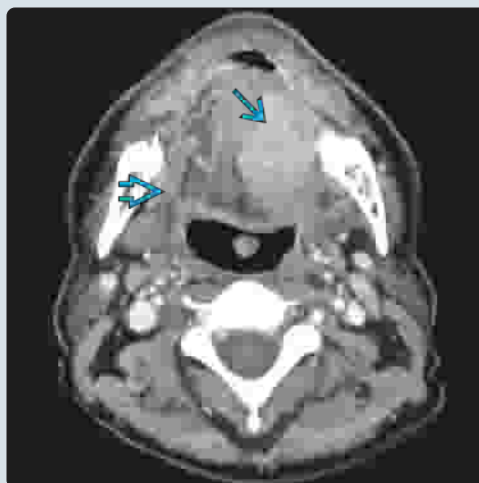


Pattern of Invasion: Small Tumor Islands



CT of Advanced Tongue Squamous Cell Carcinoma

(Left) Axial CT shows the modestly enhancing left oral tongue tumor involving the left base of the tongue with obvious involvement of the left hyoglossus muscle. Note the normal-appearing right hyoglossus muscle. (Right) PET scan of a 35-year-old man with lateral tongue cancer presents at an advanced stage (stage IV) with numerous cervical lymph nodes. Lateral tongue SCC is the most common location in patients ≤ 40 years old, accounting for 80% of all oral cavity SCCs.



Stage IV Oral Tongue Squamous Cell Carcinoma



TERMINOLOGY

Abbreviations

- Squamous cell carcinoma (SCC)
- Verrucous squamous cell carcinoma (VSCC)

Definitions

- Malignant neoplasm arising from squamous epithelium

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Tobacco use
- Betel quid (Paan): Combination of areca palm nuts, betel leaf, slaked lime, ± tobacco
 - Commonly used in South Asia
- Alcohol consumption
- Radiation exposure (ultraviolet and therapeutic)
- Syndromes associated with elevated risk of SCC
 - Fanconi anemia
 - Iron deficiency (Plummer-Vinson)
 - Li-Fraumeni syndrome

Infectious Agents

- Human papillomavirus (HPV), high-risk type associated with development of oropharyngeal (tonsil and base of tongue) carcinomas but present only in a minority of oral SCC
 - HPV-associated oral intraepithelial neoplasia in subset of oral leukoplakias

Immunosuppression

- HIV/AIDS patients have increased risk
- Organ transplant recipients

Precursor Lesions

- Can develop from area of leukoplakia or erythroplakia
 - Malignant transformation of severe dysplasia or carcinoma in situ

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~ 45,700 new cases per year in USA (includes oropharynx)
 - > 400,000 new cases per year worldwide (includes pharynx)
 - Highest rates in South Asia, account for 30% of all new cancer cases
- Age
 - Median: 62 years
 - Range: < 20-100 years
- Sex
 - Male > female (2-3:1)
 - Male:female ratio has decreased as more women smoke tobacco
- Ethnicity
 - Black < white (14.8/100,000 vs. 15.5/100,000) (USA men)
 - Incidence in blacks have been declining since 1990s; lower incidence due in part to rising incidence of HPV-associated cancers in whites
 - Survival differences: 5-year survival in white vs. black men is 67% and 45%, respectively

Site

- Tongue (lateral and ventral) accounts for > 50% of cases
- Floor of mouth
- Lip (> 90% found on lower lip)
- Retromolar trigone
- Gingiva, buccal mucosa, palate less common in USA

Presentation

- Difficulty eating and swallowing; weight loss
- Sore that does not heal
- Loose teeth or dentures that fit poorly
- Earache

Treatment

- Surgical approaches
 - Surgery remains mainstay of treatment of oral SCC ± lymph node dissection
 - Sentinel node biopsy: Used for staging clinically N0 neck
 - Technically challenging procedure
- Adjuvant therapy
 - Induction and postoperative chemotherapy sometimes used
 - Few standardized control studies of oral cavity SCC
- Radiation
 - Postoperative radiotherapy indicated in patients with high risk of locoregional recurrence

Prognosis

- Disease-free survival and overall survival correlates with TNM staging
 - Stage 1-2: 5-year survival (73%)
 - Stage 3: 5-year survival (64%)
 - Metastatic disease at presentation: 5-year survival (34%)
- 5-year survival has improved over past 20 years
 - Improvement attributed to advances in treatment
 - Some of improved survival statistics due to HPV-related subsites, which have overall more favorable prognosis
- Lip: Overall 5-year survival (89%)
- 2nd primary tumors
 - ~ 10% increased risk of 2nd aerodigestive malignancy
 - Smokers have 5-fold increased risk
 - May represent new tumor or arise in same area (field effect)
- Resection margins
 - Positive surgical margins associated with decrease in overall survival
- Lymph-vascular and perineural invasion
 - Associated with increased local recurrence and poorer overall survival
- Regional lymph node metastases
 - Associated with decrease in overall survival
 - Tumor thickness > 3 mm of lateral tongue cancer increases risk of nodal spread
 - Measurement taken from presumed original surface level to deepest tumor invasion
- Extracapsular spread in lymph node metastases
 - Associated with locoregional and distant metastases and poorer overall survival
- Advanced age associated with poorer prognosis

IMAGING

General Features

- CT &/or MR for preoperative tumor staging and treatment planning
- Chest CT or plain film to rule out lung metastases
- PET in evaluating distant metastases
 - Distant metastases uncommon in oral cavity cancer at presentation

MACROSCOPIC

General Features

- Leukoplakia, erythroleukoplakia, or erythroplakia
 - Often cannot be distinguished clinically from hyperkeratoses or dysplasia
- **Exophytic** growth pattern
 - Tumor mass can be fungating, papillary, or verruciform
 - Surface often ulcerated
 - May be friable or firm
 - Typical growth pattern for verrucous carcinoma and carcinoma cuniculatum
- **Endophytic** growth pattern
 - Depressed, ulcerated lesion that is indurated
 - May see rolled border

MICROSCOPIC

Histologic Features

- Majority are conventional keratinizing SCC type
- Histologic grade includes well-, moderately, and poorly differentiated SCC
- Adjacent areas of dysplasia or carcinoma in situ (CIS) can be identified
 - Invasion can be seen **without** any surface atypia
- **Patterns of invasion**
 - Superficial or microinvasive carcinoma
 - Basement membrane violated and tumor cells present in superficial lamina propria
 - Tumor depth only 1-2 mm as measured from adjacent intact basement membrane
 - Broad pushing front: Large tumor islands with well-defined margin
 - Jagged or irregular finger-like extensions into lamina propria
 - Small tumor islands, single filing pattern, individual cell infiltration, and widely dispersed pattern of infiltration
 - Pattern of infiltration is associated with prognosis
 - Irregular or jagged cords or small scattered tumor islands have worse prognosis
- Variable degrees of squamous differentiation
 - Dyskeratosis and squamous pearls; pleomorphism
 - Mitoses, including atypical mitoses
- Perineural invasion should be documented
 - Correlates with recurrence and survival and impacts management
- Mitotic figures and necrosis increases with grade
- Inflammatory infiltrate
 - Lymphoid infiltrate at tumor/host interface common
 - Can appear lichenoid
 - Variable number of eosinophils

- Tumor spread influenced by anatomic location
 - Tongue SCC can spread beneath intact mucosa, involving deeper intrinsic muscles
 - Gingival carcinoma can invade bone via periodontal ligament
 - Alveolar SCC in edentulous can invade bone directly through marrow spaces as bone resorbs intact cortex
 - Tumor can spread posteriorly in mandible along inferior alveolar nerve
 - Lip cancer spreads superficially in early stages
 - Advanced cases can invade mandible
 - Floor of mouth SCC spreads superficially in early stages but then extends into sublingual gland and mylohyoid muscle
 - Palatal tumors spread superficially

Lymphatic/Vascular Invasion

- Should be documented as it correlates with prognosis

Margins

- Margins (including bone) must be reported
- Shrinkage of up to 50% must be taken into consideration
 - Particularly true of lateral tongue carcinoma where there is marked postsurgical retraction of muscle
- Bone beneath tumor needs to be sampled for invasion
 - Superficial erosion of mandible/maxilla does not constitute bone invasion and does not change stage

Lymph Nodes

- All lymph nodes removed should be evaluated
- Lymph nodes should be reported by level if identified surgically
- Presence of extracapsular spread (macroscopic/microscopic) should be reported

Variants of Keratinizing Squamous Cell Carcinoma

- **Verrucous squamous cell carcinoma**
 - > 75% of all VSCC are found in oral cavity
 - Marked epithelial hyperplasia with broad elongated rete with pushing border
 - Papillary surface with marked keratosis, keratin plugging, parakeratotic crypting
 - Normal epithelial maturation with little cytologic atypia
 - Mitoses rare and observed in basal/parabasal layer
 - Dense lymphoplasmacytic host response
 - Extensive sampling to rule out conventional-type SCC, which can occur in 20% of VSCC
- **Carcinoma cuniculatum**
 - Proliferation of epithelium with endophytic growth pattern with deeply penetrating crypts filled with keratin
 - Slow-growing but deeply invasive; can burrow into bone or erode adjacent soft tissue structures
 - Little to no cytologic atypia
- **Spindle cell "sarcomatoid" squamous cell carcinoma**
 - More common in larynx and pharynx
 - Often appears polypoid
 - Pleomorphic cells arranged in fascicles with numerous mitoses
 - May see CIS overlying tumor or areas of more conventional SCC
- **Basaloid squamous cell carcinoma**
 - More common in oropharynx, hypopharynx, and larynx

- o Superficial tumor shows typical squamous differentiation
- o Deeper tumor composed of sheets of basaloid cells with palisading of peripheral cells
- o Central (comedo) necrosis
- o High mitotic rate
- **Papillary squamous cell carcinoma**
 - o Rarely found in oral cavity except as component of more conventional SCC
- **Acantholytic squamous cell carcinoma (pseudoglandular or adenoid)**
 - o Uncommon in oral cavity: Most reported on lower lip
 - o Superficial area resembles conventional SCC
 - o Deeper tumor has gland-like structures with scattered acantholytic cells

ANCILLARY TESTS

Frozen Sections

- Useful to assess surgical soft tissue margins
- **Pitfalls**
 - o Frozen section assessment of bone margins is problematic but imprints shown to be reliable indicator of margin status
 - o Small specimen &/or poor orientation may result in over/under interpretation
 - o Difficult to grade dysplasia by frozen section
 - Tissue distortion and artifactual changes make grading dysplasia challenging
 - Hyperplasia or pseudoepitheliomatous hyperplasia can be misinterpreted
 - Reactive epithelial changes adjacent to ulcer
 - Radiation changes: Knowledge of prior radiation is paramount
 - o Juxtaoral organ of Chievitz
 - Normal structure located bilaterally at angle of mandible (retromolar trigone area)
 - Composed of nonkeratinizing, bland, uniform epithelial cells surrounded by basaloid cells associated with small nerves
 - Awareness of structure important to avoid misinterpretation of perineural invasion

Immunohistochemistry

- **Positive:** Cytokeratin (CK) markers (pancytokeratin and high molecular weight CK), p40, p63
- High-grade tumors: Low molecular weight CK, CK8, CK18, CAM5.2, CK5/6 (cytoplasmic)
- **Negative:** CK7 and CK20
- p53 (nuclear) is associated with a poor prognosis
 - o p53 (nuclear) overexpression, although in poorly differentiated SCC there may be little to no expression

Genetic Testing

- Loss of heterozygosity commonly noted at 3p (*FHIT*), 9p (*CDKN2A*), 17p (*TP53*)
- Mutations in *TP53* (P53), tumor suppressor gene located on short arm of 17, increases with tobacco smoking
 - o *TP53* mutations associated with decreased overall survival, increased locoregional recurrence rates, and decreased response to therapy

- Clonal proliferation of epithelial cells that harbor genetic mutations in 1 or more fields account for field cancerization that occurs in upper aerodigestive tract
 - o Mutated *TP53* patches can be identified in mucosa adjacent to completely resected cancers, which may explain in part local tumor recurrences
- Overexpression of epidermal growth factor receptor (EGFR) correlates with increased local recurrence and worse overall survival
- To date, clinical trials using targeted therapy have yet to show significant clinical results

DIFFERENTIAL DIAGNOSIS

Pseudoepitheliomatous Hyperplasia

- Benign reactive process lacking cellular atypia and nuclear pleomorphism

Necrotizing Sialometaplasia

- Requires adequate biopsy, since overlying epithelium can exhibit pseudoepitheliomatous hyperplasia

Radiation Changes

- Can see marked pleomorphism of epithelial, endothelial, and stromal cells; may require cytokeratin markers

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Clinical stage is most important predictor of prognosis
 - o > 75% of oral SCC are diagnosed at advanced stage (III, IV), accounting for overall poor prognosis
 - o Patients have increased risk of developing 2nd primary tumor of upper aerodigestive tract

Pathologic Interpretation Pearls

- Regardless of SCC variant, all are staged similarly

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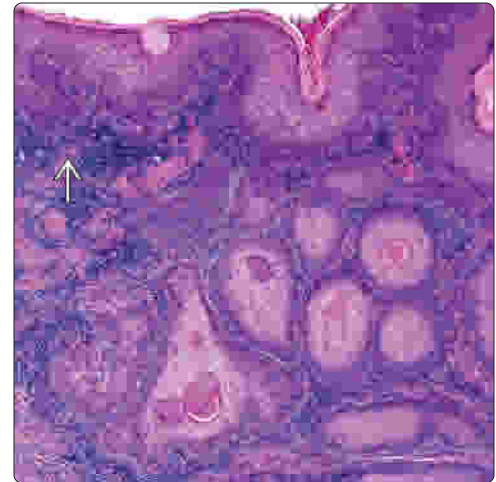
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Keratin Pearl Formation

(Left) Well-differentiated SCC shows islands of malignant epithelial cells arising from the overlying epithelium invading into the lamina propria with keratin pearl formation. **(Right)** SCC of the tongue with a prominent lymphocytic host response and keratin pearl formation is shown. The band-like lymphocytic infiltrate subjacent to the surface basal cells can mimic lichen planus; in a superficial biopsy, close scrutiny is required to rule out dysplasia.



Lymphocytic Host Response in Squamous Cell Carcinoma

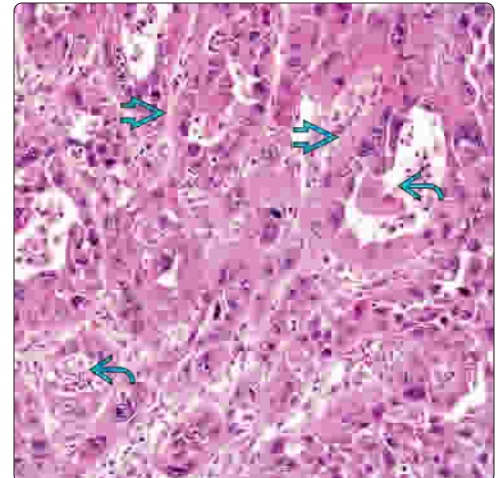


Moderately Differentiated Squamous Cell Carcinoma

(Left) Moderately differentiated SCC characterized by anastomosing strands of epithelial cells with little keratin pearl formation and cellular and nuclear pleomorphism is shown. **(Right)** Poorly differentiated SCC of the lower lip is seen with an acantholytic appearance in the deeper portion of tumor characterized by tumor nests with a glandular appearance lined by squamous epithelium. The central spaces can contain acantholytic or dyskeratotic cells or cellular debris.



Pseudoglandular Squamous Cell Carcinoma

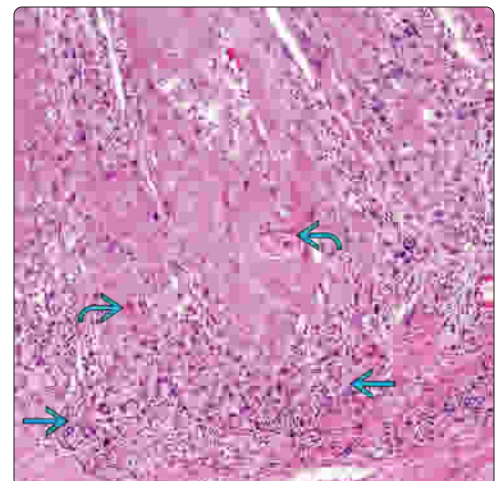


Carcinoma Cuniculatum

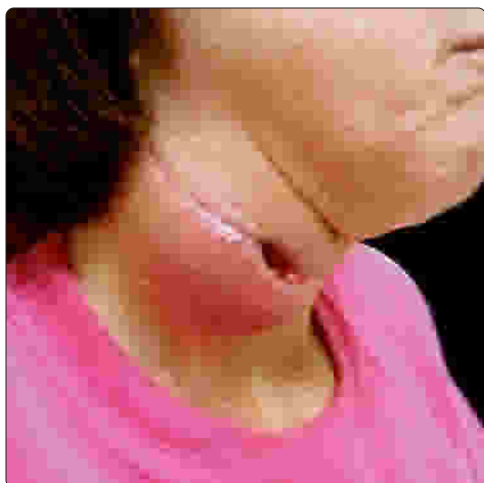
(Left) An indolent and histologically unique SCC, carcinoma cuniculatum, is characterized by keratin-filled crypts extending deep into the connective tissue. The lesion shows an endophytic proliferation. **(Right)** Higher magnification shows violation of the basement membrane by scattered tongues of malignant epithelial cells associated with an inflammatory cell infiltrate. Individual dyskeratotic cells are scattered throughout. These features distinguish this entity from verrucous carcinoma.



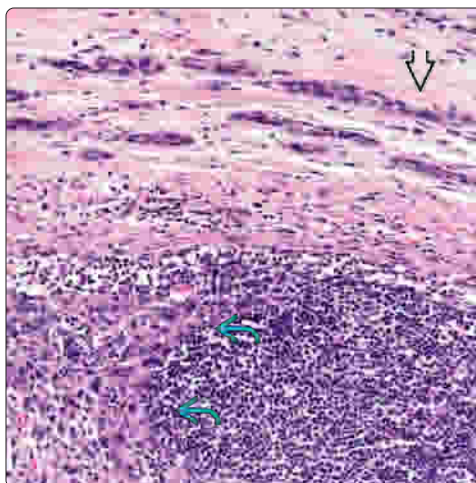
Carcinoma Cuniculatum



Persistent Metastatic Squamous Cell Carcinoma With Fistula

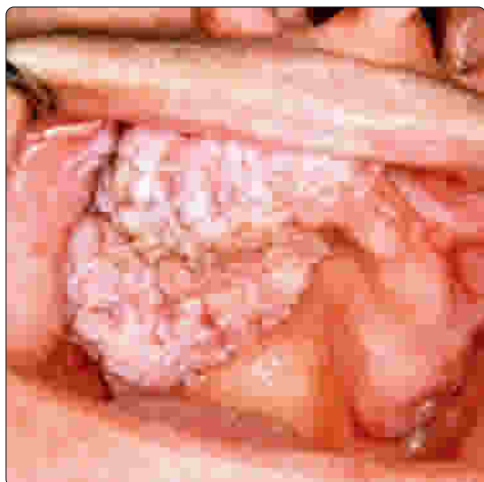


Extracapsular Lymph Node Extension

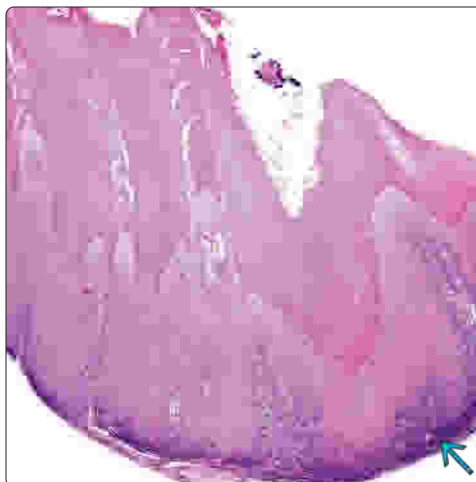


(Left) A neck dissection from this patient shows extracapsular spread of SCC in a cervical lymph node. Despite postoperative radiation, persistent tumor growth is evident and is associated with a cutaneous fistula. (Right) Extracapsular spread in a cervical lymph node is characterized by SCC is present within the lymph node [blue box] and also outside the capsule [green box]. Extracapsular spread is an independent indicator of recurrent neck disease as well as overall patient survival.

Verrucous Carcinoma (VC) of Maxilla



Verrucous Hyperkeratosis and Bulbous Rete

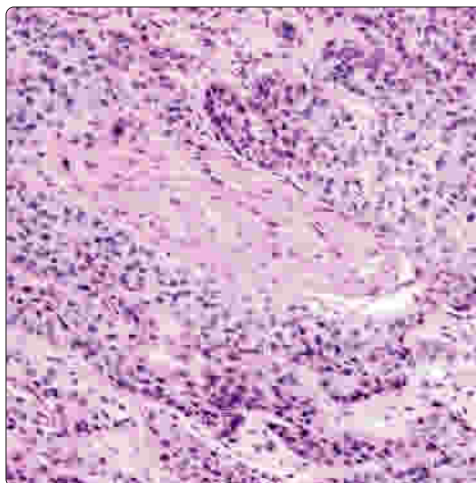


(Left) Verrucous SCC (VSCC) of the maxilla is seen presenting as a well-demarcated carpet of epithelium with papillary projections with a lateral spread. The presence of surface ulceration in VC may indicate a conventional SCC component. (Right) Broad-based epithelial proliferation with marked parakeratosis with keratin plugging is shown in VSCC. Epithelium extends deeper into the submucosa than adjacent epithelium but without invasion. The bulbous rete ridges are associated with an inflammatory cell infiltrate at the tumor front [blue box].

No Cytologic Atypia in Verrucous Squamous Cell Carcinoma



Perineural Invasion



(Left) A higher power image of VSCC illustrates the broad, thickened epithelial rete, which lacks any cytologic atypia and exhibits a normal maturation. Compare both the architectural and cytologic differences to carcinoma cuniculatum. (Right) Moderately differentiated SCC is seen surrounding a large caliber nerve. Perineural invasion is an adverse prognostic factor associated with recurrence and decreased survival.

KEY FACTS

TERMINOLOGY

- Malignant epithelial neoplasm of oropharynx, including soft palate, tonsils, uvula, base of tongue, and oropharyngeal wall comprising Waldeyer ring

ETIOLOGY/PATHOGENESIS

- High-risk HPV associated with > 80% of OPSCC cases

CLINICAL ISSUES

- OPSCC increased 1-2% annually in USA males in past 20 years, while rates of oral cavity carcinoma have decreased
- Age: Early to mid 50s; ↑ incidence in younger cohorts
- Male > > female (4-5:1)
- Enlarged cervical lymph node often presenting symptom
- > 70% of patients present with stage III or IV disease

MICROSCOPIC

- **HPV-positive OPSCC:** Nonkeratinizing histology
 - Tumor often seen arising from epithelium of tonsillar crypts

- Squamous maturation and focal areas of keratinization can be seen but should comprise < 10% of tumor

- **Lymphoepithelial-like OPSCC:** Similar to EBV-related nasopharyngeal carcinoma
 - p16(+) and EBV(-)
- **HPV-negative OPSCC:** Exhibits features of conventional-type SCC

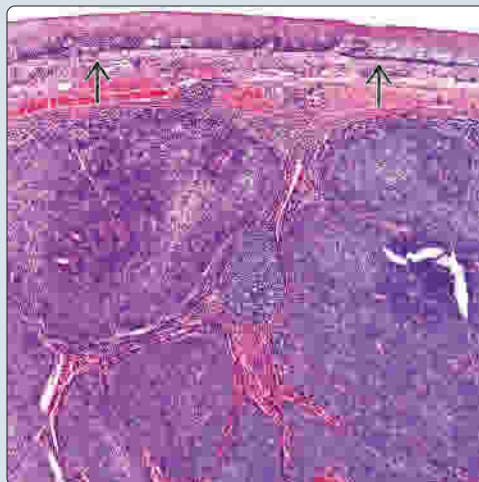
ANCILLARY TESTS

- p16 strongly **positive** in HPV-associated OPSCC
- HPV 16 ISH correlates with p16 IHC
- HPV ISH mRNA E6/E7 concordant with p16 IHC

TOP DIFFERENTIAL DIAGNOSES

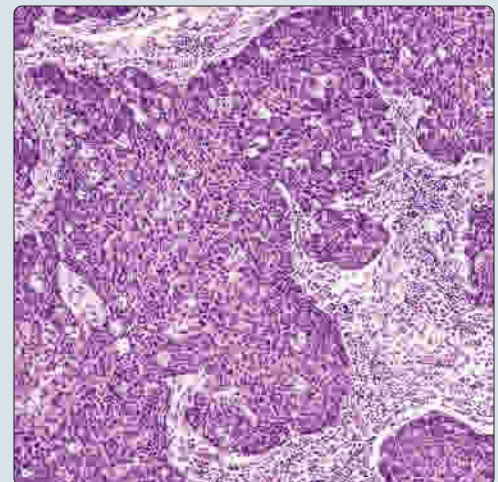
- **Basaloid squamous cell carcinoma:** Highly aggressive tumor; propensity for oropharynx, hypopharynx, larynx
- **Nasopharyngeal carcinoma:** Similar clinical presentation of enlarged cervical lymph node as initial manifestation of disease; strong association with Epstein-Barr virus; in situ hybridization for Epstein-Barr encoded RNA (EBER) (+)

Oropharyngeal Carcinoma



(Left) HPV-related nonkeratinizing SCC of the tonsil typically arises in the tonsillar crypts and the surface epithelium will often show no dysplastic changes [2]. Note the marked basaloid appearance of the tumor. (Right) Typical microscopic features of nonkeratinizing SCC of the tonsil are seen with sheets and nests of basaloid tumor cells with a sharply defined borders. No stromal reaction is seen to the tumor. The cells are ovoid to spindled with minimal squamous maturation.

Nonkeratinizing Type of OPSCC

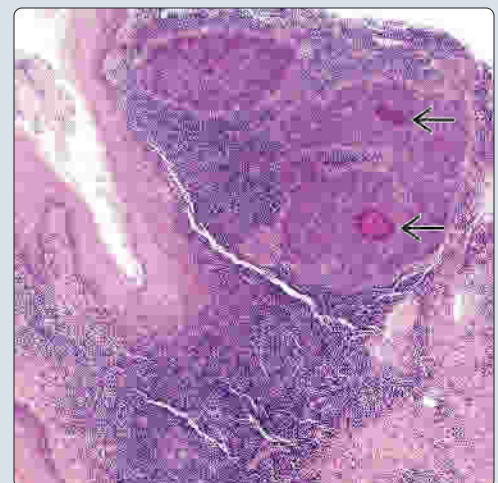


Carcinoma Transition at Surface



(Left) In this example of an HPV-associated oropharyngeal carcinoma, a transition can be seen in the surface epithelium, with an abrupt [2] demarcation noted. This is not a common finding. (Right) There is an intimate association of the neoplastic islands with the surrounding lymphoid stroma. Isolated areas of keratinization are noted [2], but < 10% of the tumor volume.

Focal Keratinization



TERMINOLOGY

Abbreviations

- Oropharyngeal squamous cell carcinoma (OPSCC)

Definitions

- Malignant epithelial neoplasm of oropharynx, including soft palate, tonsils, uvula, base of tongue, and oropharyngeal wall comprising Waldeyer ring

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Tobacco use reported in 50-75% HPV-positive OPSCC
 - Smoking may either increase risk of HPV infection or persistence

Infectious Agents

- High-risk HPV associated with > 80% of cases of OPSCC
 - HPV serovar 16 is predominant type (> 90%), although other HPV high-risk types are reported

Sexual History

- Number of oral sex partners strong risk factor

CLINICAL ISSUES

Epidemiology

- Incidence
 - OPSCC increased 1-2% annually in USA males in past 20 years, while rates of oral cavity carcinoma have decreased
- Age
 - Median: Early to mid 50s
 - Increasing incidence in younger cohorts
- Sex
 - Male > > > female (4-5:1)
- Ethnicity
 - HPV-positive OPSCC more common in whites

Site

- Anterior tonsillar pillar and fossa most common site followed by tongue base

Presentation

- Early lesions generally asymptomatic
- Tonsillar asymmetry
- Dysphagia, otalgia, trismus
- Enlarging cervical lymph node
 - Often presenting symptom
- > 70% of patients present with stage III or IV disease

Treatment

- Multiple approaches depending on clinical stage
 - Minimally invasive surgical techniques
 - Transoral robotic surgery (TORS)
 - Transoral laser microsurgery
 - Radiation therapy including intensity-modulated radiation therapy (IMRT)
 - Concurrent radiotherapy with multiagent chemotherapy
 - Targeted agents such as cetuximab
 - Salvage neck dissection when indicated

Prognosis

- HPV-positive OPSCC associated with improved outcomes
 - 5-year survival: > 69%
- Tumor size and presence of metastases influence prognosis

IMAGING

General Features

- PET/CT useful particularly when approaching unknown primary

MACROSCOPIC

General Features

- Exophytic or ulcerative
- Base of tongue primary SCC can be deeply infiltrative with extension to oral tongue, vallecula, epiglottis, preepiglottic space, and tonsils
- Cystic lymph node metastases

Sections to Be Submitted

- Entire tonsil should be submitted when trying to identify clinically occult primary &/or no mass noted grossly

MICROSCOPIC

Histologic Features

- **HPV-positive OPSCC**
 - **Nonkeratinizing OPSCC**
 - Tumor often seen arising from tonsillar crypt epithelium rather than surface epithelium
 - Basaloid oval to spindle-shaped cells with hyperchromatic nuclei and minimal cytoplasm forming trabeculae, sheets, or nests with sharply defined borders
 - Comedonecrosis frequently present
 - Brisk mitotic rate and numerous scattered apoptotic cells
 - Permeated by lymphocytes
 - Squamous maturation and focal areas of keratinization may be seen but must comprise < 10% of tumor volume
 - **Hybrid-type OPSCC (with maturation)**
 - Has features of both nonkeratinizing and keratinizing OPSCC
 - Basaloid tumor cells undergo focal and partial keratinocytic maturation
 - Amount of squamous maturation is > 10% but < 25%
 - Slightly fewer cases are p16 or HPV-ISH positive than nonkeratinizing type
 - **Lymphoepithelial-like OPSCC**
 - Similar in histology to EBV-related nasopharyngeal carcinoma
 - Syncytial-appearing large tumor cells with indistinct cell borders and vesicular nuclei intermingled with lymphocytes and plasma cells
 - Tumor cells immunoreactive for cytokeratin
 - **Positive:** p16; **negative:** Epstein-Barr encoded RNA (EBER)
 - **Papillary OPSCC**
 - Uncommon morphologic variant of SCC that can occur in oropharynx

- Finger-like projections of cytologically malignant epithelial cells with fibrovascular cores
- Surface keratinization absent or limited
- Definitive invasive SCC may be difficult to see, particularly on biopsy specimens
- ~ 65% positive for p16 and ~ 50% positive for high-risk HPV by RNA ISH

- **HPV-negative OPSCC**

- **Keratinizing SCC**

- Exhibits features of conventional-type SCC, including nests of epithelial cells with abundant eosinophilic cytoplasm and well-defined cell borders
 - Basaloid morphology not seen
 - Tumors divided into well, moderately, and poorly differentiated
 - < 20% are p16 positive

ANCILLARY TESTS

Cytology

- Fine-needle aspiration of cervical lymph node may be initial evaluation
 - Nonkeratinizing OPSCC shows cohesive groups of cells with distinct cell borders and hyperchromatic nuclei
 - Keratinization absent or minimal
 - Cellular debris and inflammatory cells
 - May be hypocellular because of cyst formation
 - Serous fluid in cystic lymph node metastasis
 - Distinct from metastatic lymph node with central necrosis

Immunohistochemistry

- **Positive:** p16 in HPV-associated OPSCC
 - > 70% of tumor cells with nuclear and cytoplasmic staining
 - Normal epithelium is **negative** or shows minimal patchy staining
 - p16 considered reliable surrogate marker for high-risk HPV-associated OPSCC
- p16 useful on FNA cell block from occult neck mass to help localize tumor origin to oropharynx
- Strongly **positive** with cytokeratin(s)
 - Usually not required for diagnosis except in lymphoepithelial-like variant

In Situ Hybridization

- HPV 16 correlates with p16 immunohistochemistry
 - **Positive:** Nuclear dots, which may range from strongly and diffusely positive to only a rare positive cell
 - Single punctate nuclear dot or multiple nuclear dots in tumor cell
 - Not detected in normal tonsillar epithelium
 - May see hybridization signals in dysplastic epithelium
- HPV ISH mRNA E6/E7 concordant with p16 IHC
- Other HPV types have been detected, including HPV 6, 18, 33, 35, 45, and 52/58
- HPV ISH can be used on FNA cell block from metastatic lymph node

DIFFERENTIAL DIAGNOSIS

Basaloid Squamous Cell Carcinoma (BSCC)

- Highly aggressive tumor with propensity for oropharynx, hypopharynx, and larynx
- Growth pattern includes lobules and trabeculae that form jigsaw configuration
- Pleomorphic basaloid cells with numerous mitoses with peripheral nuclear palisading
- Hyaline or mucohyaline material may be seen intercellularly
 - Similar to duplicated basement membrane material in some salivary gland neoplasms
- Prominent comedo-type necrosis
- Squamous component is minor component and may be seen as dysplasia, CIS, or invasive SCC
- Frequent metastases to regional lymph nodes and lung
- **Positive:** Cytokeratins, variable with vimentin, neuron-specific enolase, S100 protein, and actins
- Poor prognosis
 - Detection of HPV in BSCC from oropharynx is associated with better prognosis

Nasopharyngeal Carcinoma (NPC)

- Share similar clinical presentation of enlarged cervical lymph node as initial manifestation of disease
 - Strong association with Epstein-Barr virus (EBV)
 - EBER may help with separating occult metastasis from nasopharynx or oropharynx

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- When evaluating cystic neck mass in older individual, 1st diagnostic consideration should be cystic metastasis from oropharyngeal primary
 - Branchial cleft cysts are unusual in patients over 50 years of age
 - Typically p16 negative, but may overexpress p16, necessitating molecular analysis for HPV
 - Presence of HPV would support metastatic carcinoma
- OPSCC must be evaluated for p16/HPV as positive tumors have better prognosis

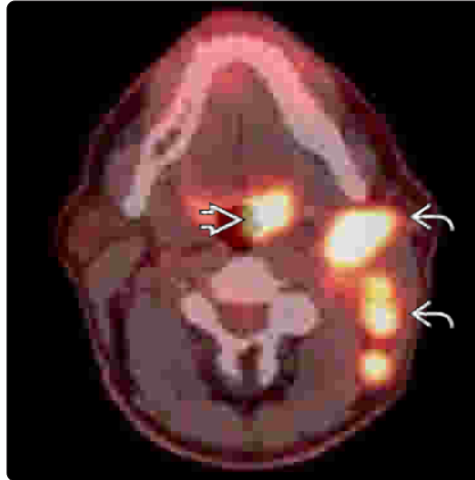
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Papillary Variant of OPSCC

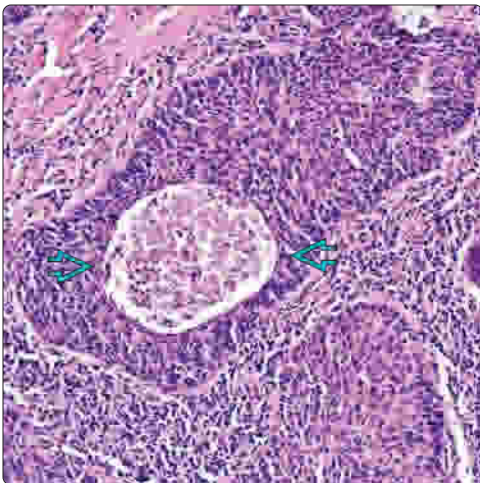


Cervical Lymph Node Metastases

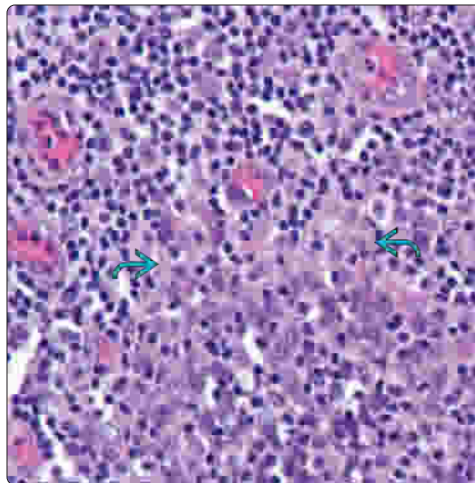


(Left) This is an unusual HPV-positive papillary variant of oropharyngeal squamous cell carcinoma in a 42-year-old white male. Most reported cases were in younger patients, had nonkeratinizing morphology, and are usually p16 positive. (Right) Patients with tonsil SCC (OPSCC) often present clinically at an advanced stage as seen on this fused PET/CT, which shows the primary in the tonsil along with numerous lymph node metastases in the cervical lymph node chain.

Nonkeratinizing OPSCC

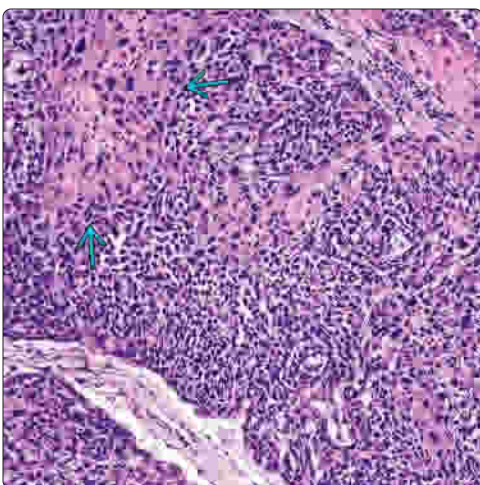


Lymphoepithelial-Like Variant of OPSCC

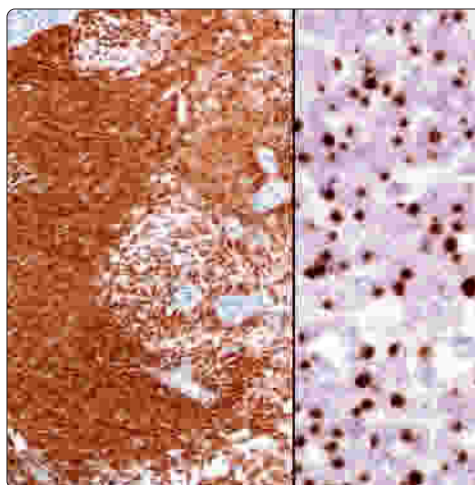


(Left) A common finding in nonkeratinizing SCC of the tonsil is comedo-type necrosis as well as apoptosis and mitoses. These features should not be misinterpreted as basaloid squamous cell carcinoma. (Right) A morphologic variant of HPV-related OPSCC is lymphoepithelial-like carcinoma, which is indistinguishable from nonkeratinizing nasopharyngeal carcinoma. The tumor cells have indistinct cell borders with a syncytial growth pattern and lymphoplasmacytic infiltrate.

Hybrid Variant OPSCC



p16 Immunohistochemistry and HPV ISH



(Left) Focal keratinization can be identified in some nonkeratinizing SCC of the tonsil but make up < 25% of the tumor. Hybrid lesions can show basaloid morphology in the center with squamous differentiation toward the periphery. (Right) HPV-related nonkeratinizing SCC shows strong, diffuse nuclear and cytoplasmic immunoreactivity with p16 (left panel). In situ hybridization with HPV16/18 shows a strong signal characterized by nuclear dots (right panel).

KEY FACTS

TERMINOLOGY

- Malignant neural crest-derived neoplasm with melanocytic differentiation

CLINICAL ISSUES

- Extremely rare accounting for < 1% of all melanomas
 - Represent < 0.5% of all oral malignancies
- Mean in 6th-7th decades
- Male > female (2.5-3:1)
- Hard palate and maxillary alveolus are most common sites of involvement (~ 80%)
- Cervical lymph node metastases reported > 50% of cases at presentation
- Asymmetric, painless, pigmented lesion with irregular borders
- Radical surgical excision
- Overall, poor prognosis (median: 2 years)

IMAGING

- Oral cavity mass with high T1 signal on MR

MICROSCOPIC

- In situ component with pagetoid spread of single or multiple melanoma cells in superficial epithelium
- Epithelioid or spindle-shaped morphology of melanocytes containing fine melanin granules
 - 15% of oral melanomas have little to no melanin
- 1/3 of cases have bone/cartilage invasion

ANCILLARY TESTS

- **Positive:** S100 protein, SOX10, HMB-45; tyrosinase, melan-A, MITF

TOP DIFFERENTIAL DIAGNOSES

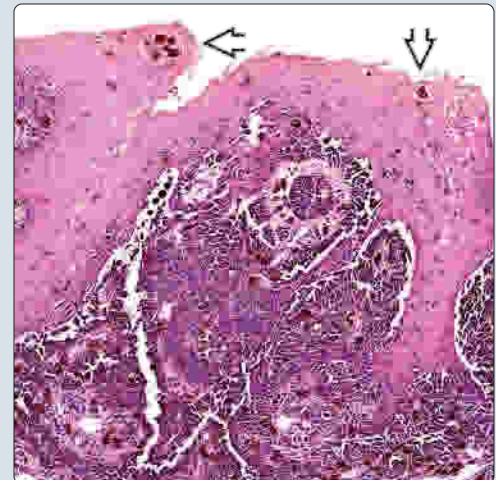
- Spindle cell squamous cell carcinoma, metastatic melanoma, pleomorphic sarcoma

Palatal MM With Satellite Lesions

(Left) Primary melanoma of the hard palate presents as a diffuse, patchy area of heavy pigmentation with irregular borders. Satellite lesions are noted away from the main area of pigmentation. **(Right)** Nodular melanoma of the hard palate shows epithelioid malignant melanocytes, some with melanin pigment, expanded into the lamina propria. Individual melanocytes (Pagetoid spread) are seen in the upper layers of the mucosa.



Epithelioid Melanocytes in Nodular MM

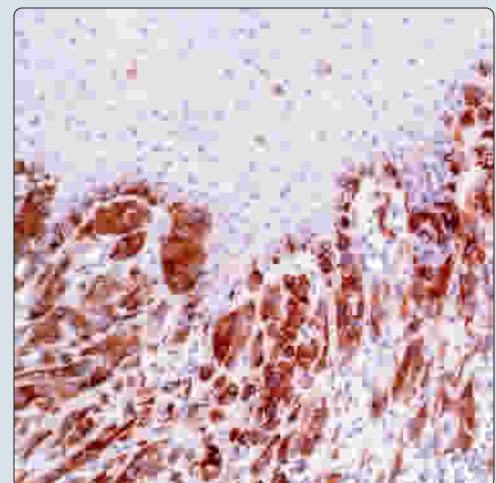


Pseudoepitheliomatous Hyperplasia in MM

(Left) There is a concurrent pseudoepitheliomatous hyperplasia present in association with an atypical melanocytic proliferation. An inflammatory infiltrate is also present. The melanoma may be obscured or missed due to this process. **(Right)** HMB-45 immunohistochemistry highlights the melanocytes present both in the basal layer as well as in the submucosa. This is one of the more specific markers for melanoma. It is important to know that staining can be patchy or focal.



HMB-45 Highlights Melanocytes



TERMINOLOGY

Definitions

- Malignant neural crest-derived neoplasm with melanocytic differentiation
 - Atypical melanocytes at epithelial-connective tissue interface with upward migration or connective tissue invasion

ETIOLOGY/PATHOGENESIS

Etiology

- Unknown: Not related to preexisting mucosal nevi or physiologic pigmentation
- Increased frequency of *c-KIT* (CD117) mutations in mucosal melanomas have been reported
 - Mutation not detected in cutaneous melanomas
- BRAF mutations **not** detected in mucosal melanoma, but seen in cutaneous melanomas

CLINICAL ISSUES

Epidemiology

- Incidence
 - Extremely rare, accounting for < 1% of all melanomas
 - 0.02/100,000 population/year in USA
 - Represent about 40% of all head and neck mucosal melanomas
 - Represent < 0.5% of all oral malignancies
 - Unlike cutaneous melanoma, oral melanoma incidence has been stable
- Age
 - Mean: 6th-7th decades; rare in pediatric patients
- Sex
 - Male > female (2.5-3:1)
- Ethnicity
 - More common in Japan and western Africa

Site

- Hard palate and maxillary alveolus are most common sites of involvement (~ 80%)
- Remaining 20% include
 - Mandibular gingivae
 - Buccal mucosa
 - Floor of mouth and tongue

Presentation

- Most arise de novo, although 1/3 are preceded by pigmented lesion for a few months or years
 - Melanosis reported before development of melanoma
- Asymmetric, painless, pigmented lesion
 - Irregular borders or outlines
 - Black, purple, red, gray
 - 15% of oral melanomas are amelanotic
 - Macular, with nodular areas
- Many patients present at advanced stage with pain, ulceration, loose teeth
- Cervical lymph nodes metastases reported in up to 50% of cases at presentation
 - Lymph node metastases increase when tumor thickness > 5 mm

- Distant metastases seen in about 50% of patients at presentation

Treatment

- Surgical approaches
 - Radical surgical excision
 - Clear margins not always possible due to adjacent vital structures, resulting in local control rates of < 50%
 - Some institutions recommend regional lymph node dissection, even in clinically negative neck
- Adjuvant therapy
 - No clear cut evidence that chemotherapy or immunotherapy for oral melanoma provides any survival benefits
 - Generally used for palliative purposes
 - Not recommended as a single modality treatment
- Radiation
 - May provide prolonged palliation but does not appear to provide any survival benefits

Prognosis

- Overall, poor prognosis
 - Median survival: 2 years
 - 5-year survival: 5-10%
- High rates of metastases to liver, brain, and lung
- Worse prognosis suggested by
 - Thickness > 5 mm
 - Vascular invasion
 - Necrosis
 - Significant pleomorphism
 - Older age
 - High stage

IMAGING

MR Findings

- Best imaging study is multiplanar MR
- Oral cavity mass with high T1 signal on MR
 - Melanotic melanomas show increased signal due to melanin, free radicals, metal ions, and hemorrhage, giving high or intermediate T1 signal

MACROSCOPIC

General Features

- Brown to black pigmented lesion with irregular borders
- Flat macule extends laterally (radial growth phase); nodular lesion (vertical growth phase)
 - Some oral melanomas lack radial growth phase
- Satellite lesions of melanoma are common

Sections to Be Submitted

- Bone &/or cartilage for staging

Size

- Range: Up to 4 cm generally

MICROSCOPIC

Histologic Features

- Radial growth phase similar to junctional lentiginous melanoma

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
S100	Positive	Nuclear & cytoplasmic	Diffuse and strong
SOX10	Positive	Nuclear	Diffuse and strong
HMB-45	Positive	Cytoplasmic	Most tumor cells positive
Tyrosinase	Positive	Cytoplasmic	Variably reactive in most cases
Melan-A103	Positive	Cytoplasmic	Variably reactive in most cases
MITF	Positive	Nuclear	Positive in most cases
CD117	Positive	Cytoplasmic	Isolated tumor cells positive
NSE	Positive	Cytoplasmic	Variably present in many cases
Desmin	Negative		
CD45RB	Negative		
CK-PAN	Negative		

- o Pagetoid spread (in situ): Single or multiple melanoma cells within epithelium
- o Atypical melanocytes in basal layer spreading laterally
- o Invasion of melanoma cells into lamina propria
- o Prominent dendritic processes may be seen
- o May have pseudoepitheliomatous hyperplasia
- Nodular growth phase
 - o Epithelioid or spindle-shaped morphology to melanocytes containing fine melanin granules
 - 15% of oral melanomas have little to no melanin
 - o 1/3 of cases have bone/cartilage invasion
 - o Vascular and perineural invasion not readily noted
 - o Mitoses tend to be infrequent but are increased in invasive tumors
 - o Pleomorphic cells with atypical mitoses
 - Polygonal, spindled, epithelioid, small cell
 - Intracellular cytoplasmic inclusions, prominent nucleoli
 - o Squamous surface ulceration or atrophy is common
 - o Pseudoepitheliomatous hyperplasia adjacent to tumor may be seen

- High-grade tumors, significant pleomorphism, increased mitoses
- **Positive:** Up to 70% epithelial markers, p63, p40; **negative:** Melanoma markers

Pleomorphic Sarcoma

- High-grade spindled cell tumor, lacking surface origin or involvement
- By definition, lacks melanoma and epithelial markers

Metastatic Melanoma

- Extremely rare, with very few reported cases
- Most common: Tongue, buccal mucosa, lip
- Clinical history required
- *BRAF* or *c-KIT* useful in selected cases, but not IHC

Clinical Differential Diagnosis

- May be clinically worrisome for mucosal melanoma but can be easily separated by histologic examination
 - o **Oral nevi:** Intraoral nevi usually single and quite small
 - o **Melanoacanthoma:** Rapid growth of this benign lesion usually dictates biopsy to rule out melanoma
 - o **Physiologic Pigmentation:** Generally diffuse
 - o **Smoker's melanosis**
 - o **Amalgam tattoo**
 - o **Medication-related pigmentation:** Chloroquine & minocycline can cause oral pigmentation
 - o **Systemic diseases:** Addison disease, Peutz-Jeghers syndrome, Laugier-Hunziker syndrome

ANCILLARY TESTS

Histochemistry

- Melanin can be highlighted with Masson-Fontana or Schmorl stains

Immunohistochemistry

- **Positive:** S100 protein, SOX10, HMB-45, tyrosinase, melan-A, MITF, vimentin
- **Negative:** Pan-cytokeratin, myogenic markers, epithelial membrane antigen

Genetic Testing

- *NRAS* and *KIT* mutations have been identified in mucosal melanomas
 - o May be useful for targeted therapies

DIFFERENTIAL DIAGNOSIS

Spindle Cell Squamous Cell Carcinoma

- Should be considered when there is no pigmentation
- Junctional origin frequently present

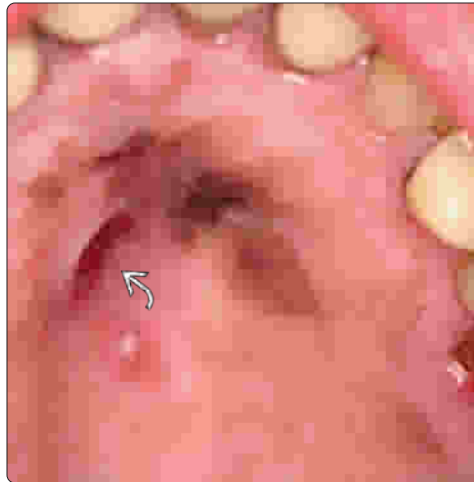
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PET Scan of Palatal Melanoma

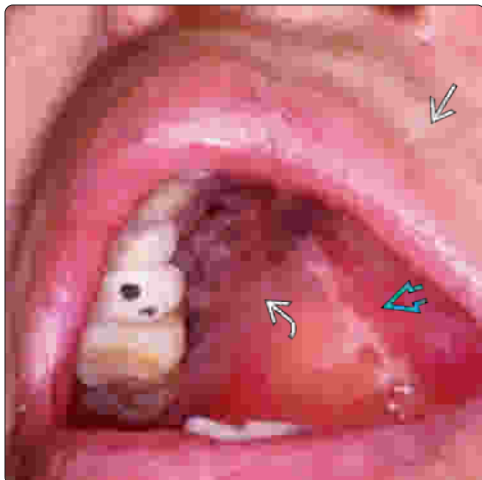


Palatal Mucosal Melanoma

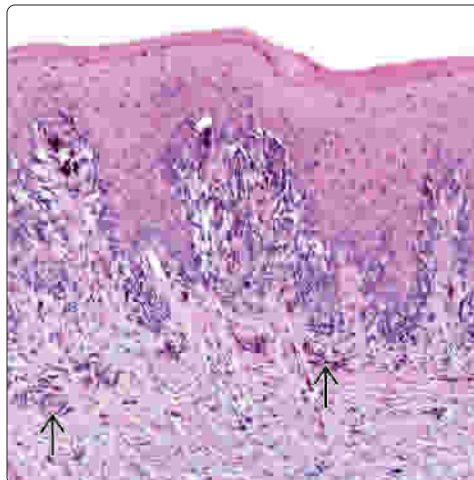


(Left) The PET scan of a palatal melanoma shows FDG uptake in the region corresponding to the pigmentation seen clinically. Although this patient had no cervical metastases, up to 75% of oral melanomas have metastases at presentation. (Right) Image shows a 65-year-old woman with newly diagnosed palatal mucosal melanoma status post punch biopsy. The hard palate and maxillary alveolus account for 80% of reported cases. Most cases are pigmented although 15% of oral melanomas are amelanotic.

Recurrent Mucosal Melanoma



Lentiginous Junctional Growth Pattern

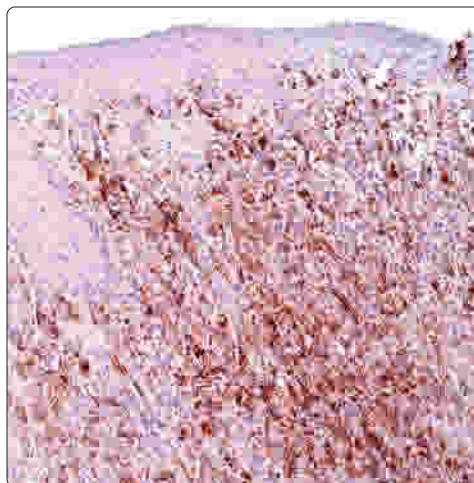


(Left) This patient had a hemimaxillectomy for palatal mucosal melanoma. The surgical scar is evident as is lack of teeth in this area resulting in lip asymmetry. The recurrence presents as numerous satellite lesions on the contralateral palate. (Right) The majority of the proliferation in this melanoma is noted at the epithelial to stromal junction. However, isolated nests of atypical melanocytes are noted within the superficial region of the stroma. Inflammatory cells are inconspicuous.

Lentiginous Junctional Pattern in MM



Strong, Diffuse S100 Protein Reaction



(Left) High-power histology shows junctional lentiginous melanoma of the hard palate with numerous atypical melanocytes present in the basal epithelium with invasion into the superficial submucosa. (Right) S100 protein shows a very strong and diffuse nuclear and cytoplasmic reactivity in the neoplastic cells as they expand from the surface epithelium into the stroma. Depth of invasion is difficult to assess for oral melanoma.

Angiosarcoma

KEY FACTS

TERMINOLOGY

- Malignant neoplasm of vascular endothelium

CLINICAL ISSUES

- Oral tumors comprise ~ 1% of all angiosarcomas
- Wide age range, with high incidence in elderly
- Male > female (1.1:1)
- Bleeding, painful mass
- Tongue > lip > gingiva > palate
- Wide local excision
- Prognosis may occasionally be favorable
- Metastasis and recurrences common: Lung, bone, and liver

MACROSCOPIC

- Invasive tumor with bloody cut surface
- Frequently multinodular

MICROSCOPIC

- Wide spectrum of histologic patterns: Vasoformative, solid, papillary
- Anastomosing vascular channels: Lined by moderately atypical endothelial cells
- Neolumen containing erythrocytes
- Large, polygonal eosinophilic cells, vesicular nuclei, prominent nucleoli
- Mitotic rate varies based on tumor grade
- Prominent necrosis is often present

ANCILLARY TESTS

- **Positive** with variety of vascular markers

TOP DIFFERENTIAL DIAGNOSES

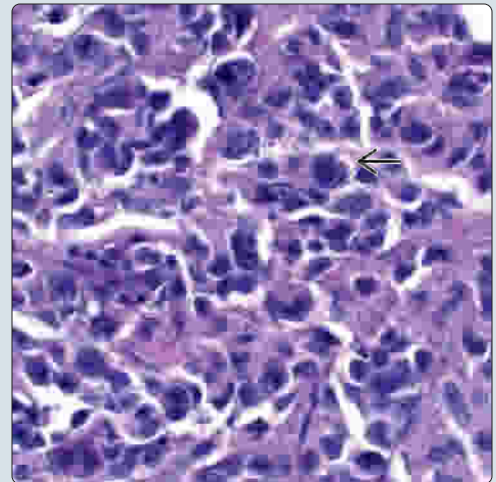
- Hemangiomas
- Spindle cell "sarcomatoid" squamous cell carcinoma
- Mucosal malignant melanoma
- Other sarcomas

(Left) This 15-year-old girl with gingival angiosarcoma presented with a bleeding mass clinically thought to be a pyogenic granuloma. Subsequent biopsy was an angiosarcoma. The patient died of her disease 2 years later. **(Right)** Poorly differentiated angiosarcoma shows atypical cells with little evidence of vascular channels. Neolumen formation is noted [B]. IHC staining (not shown) was needed to confirm the diagnosis.

Large Angiosarcoma of Gingiva

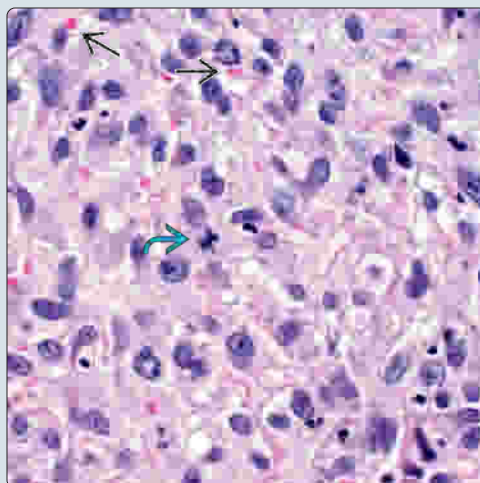


High-Power Image of Vascular Channels

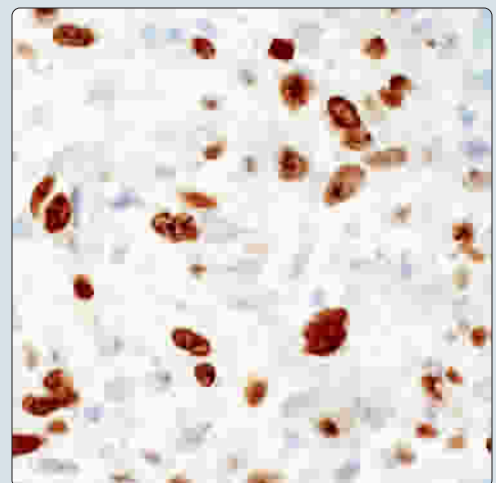


(Left) High-power image shows characteristic intracytoplasmic vacuoles (neolumen) containing red blood cells [B]. This particular tumor has a very high mitotic rate, with numerous mitotic figures [B]. The cells in this field are large and polygonal with vesicular nuclei and prominent nucleoli. **(Right)** Ki-67 shows nuclear reactivity in at least 10% of the cells. In this angiosarcoma of the buccal mucosa, the percentage of staining is much higher.

Intracytoplasmic Neolumen



High Proliferation Index With Ki-67



TERMINOLOGY

Definitions

- Malignant neoplasm of vascular endothelium

ETIOLOGY/PATHOGENESIS

Associations

- Longstanding lymphedema, radiation treatment for other neoplasms, trauma/foreign body, immune system deficiency (xeroderma pigmentosum), preexisting benign vascular neoplasms

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare; oral tumors comprise ~ 1% of all angiosarcomas
- Age
 - Wide range, with high incidence in elderly
- Sex
 - Male > female (1.1:1)

Site

- Tongue > lip > gingiva > palate; gingiva most common for secondary tumors

Presentation

- Bleeding is common, with ulcerated, pain mass, often with recent enlargement

Treatment

- Surgical approaches
 - Wide local excision
- Adjuvant therapy
 - Radiation and chemotherapy are considered ineffective

Prognosis

- Prognosis may occasionally be favorable
 - Lip and tongue primaries show relatively good prognosis
- Metastasis and recurrences common: Lung, bone, and liver

MACROSCOPIC

General Features

- Invasive tumor with bloody cut surface, red to bluish-purple
- Frequently multinodular

Size

- Range: Up to 7 cm; mean: 2.5 cm

MICROSCOPIC

Histologic Features

- Spectrum of patterns: Vasoformative, solid, papillary
- Anastomosing vascular channels: Lined by moderately atypical endothelial cells
 - Tumor cell spindling can be seen: Elongated nuclei with prominent nucleoli
- Papillary tufting often seen
- Intracytoplasmic vacuoles (neolumen) containing erythrocytes
- Epithelioid subtype: Large, polygonal eosinophilic cells, vesicular nuclei, prominent nucleoli, neolumen
- Mitotic rate varies based on tumor grade
- Prominent necrosis is often present in high-grade tumors
- Inflammatory infiltrate is usually absent or limited
- Tumor grade: Low, intermediate, high

DIFFERENTIAL DIAGNOSIS

Hemangiomas

- Lack pleomorphism and destructive growth

Spindle Cell "Sarcomatoid" Squamous Cell Carcinoma

- More common than angiosarcoma, but not vasoformative
- **Negative:** endothelial markers; **positive:** ~70% CK-pan

Mucosal Malignant Melanoma

- Similar nuclear pleomorphism and large nucleoli
- **Positive:** Melanocytic markers

Kaposi Sarcoma

- Slit-like vascular spaces, extravasated erythrocytes, intra- and extracellular hyaline globules; **positive:** HHV8, D2-40

Other Sarcomas

- **Negative:** Endothelial markers

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2. Terada T: Angiosarcoma of the oral cavity. *Head Neck Pathol.* 5(1):67-70, 2011
3. Fanburg-Smith JC et al: Oral and salivary gland angiosarcoma: a clinicopathologic study of 29 cases. *Mod Pathol.* 16(3):263-71, 2003

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
FLI-1	Positive	Nuclear	Almost all tumor nuclei
CD31	Positive	Cell membrane	More diffuse, more specific
CD34	Positive	Cell membrane	Focal
FVIIIIRAg	Positive	Cytoplasmic	Diffuse, most tumor cells
Actin-sm	Positive	Cytoplasmic	Adjacent to vascular spaces
Ki-67	Positive	Nuclear	> 10% of cells
D2-40	Equivocal		Podoplanin lymphatics >>> vascular endothelium
CK-PAN	Negative		± in soft tissue angiosarcomas (especially epithelioid variant)

KEY FACTS

TERMINOLOGY

- Locally aggressive vascular neoplasm of intermediate type, which rarely metastasizes

CLINICAL ISSUES

- Oral cavity common site for AIDS-associated Kaposi sarcoma (KS)
- Multiple reddish to purple macules that eventually develop into plaques or nodules
- Human herpesvirus 8 (HHV8) can be detected in peripheral blood and saliva

MICROSCOPIC

- Patch stage: Proliferation of small irregularly shaped vascular spaces, which often run parallel to epithelium
- Plaque stage: More vascular proliferation with spindle cell appearance; hyaline globules present
- Nodular stage: Infiltrating fascicles of spindled cells with atypia and mitoses



- Lymphangiomatous KS: Large dilated anastomosing vessels with papillary tufting imparting lymphangioma appearance

ANCILLARY TESTS

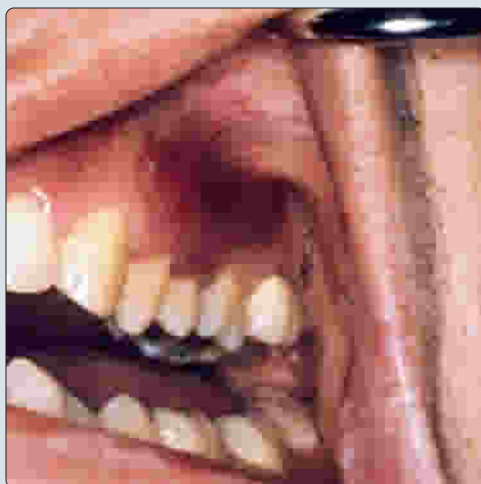
- HHV8 nuclear staining **positive** in all cases
- Spindled cells usually **positive** for CD34, CD31, and FVIIIIRAg
- Lymphatic-specific markers: D2-40, LYVE-1, VEGFR3, and PROX1

TOP DIFFERENTIAL DIAGNOSES

- Pyogenic granuloma:** Lobular, endothelial growth pattern, HHV8(-)
- Kaposiform hemangioendothelioma:** No association with HIV or HHV8 infection
- Angiosarcoma:** Marked pleomorphism, mitoses, necrosis; no HHV8
- Spindle cell squamous carcinoma:** Cytokeratin (+), HHV8(-)



(Left) A flat red-purple to brownish macule on the attached maxillary gingiva extending into the vestibule is seen in a 38-year-old HIV(+) man. Due to the location, the patient experienced bleeding from trauma. The lesion can progress to become more nodular. (Right) Kaposi sarcoma of the hard palate exhibits normal overlying mucosa and numerous vascular spaces of varying sizes in the submucosa. Erythrocytes are present within  and between the vessels .

Clinical Photo of Gingival Kaposi Sarcoma

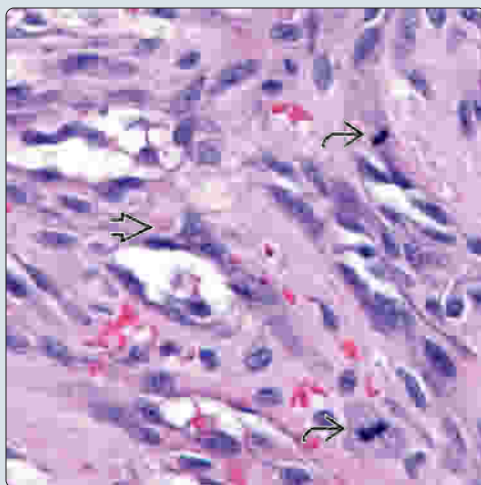


Vessels and Extravasated Erythrocytes

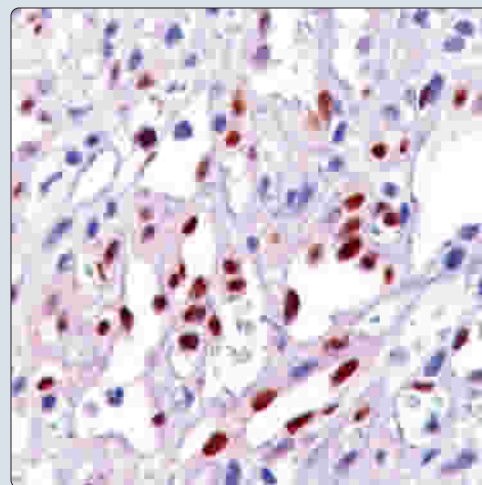


(Left) High-power photomicrograph of Kaposi sarcoma shows spindled endothelial cells forming slit-like spaces. Hyaline globules  and mitotic figures  are evident. These histologic findings are noted in both plaque and nodular stages. (Right) Spindled-shape tumor cells show strong diffuse nuclear immunoreactivity for human herpesvirus 8 (HHV8) latency-associated nuclear antigen-1. These cells are also positive for lymphatic-specific markers D2-40, VEGFR3, and PROX1.

Slit-Like Vessels in Kaposi Sarcoma



Immunoreactivity for HHV8



TERMINOLOGY

Abbreviations

- Kaposi sarcoma (KS)

Definitions

- Locally aggressive vascular neoplasm of intermediate type, which rarely metastasizes

ETIOLOGY/PATHOGENESIS

Etiology

- Uniformly associated with KS-herpes virus (KSHV), γ 2-herpesvirus (human herpesvirus 8 [HHV8])
- HIV-induced immunosuppression is important cofactor

CLINICAL ISSUES

Epidemiology

- Incidence
 - AIDS-associated KS: Up to 20% of HIV(+) patients
- Age
 - AIDS-associated KS: 4th or 5th decade
- Sex
 - Primarily homosexual and bisexual HIV-1(+) men

Site

- Oral cavity is common site for AIDS-associated KS
 - 70% of patients with cutaneous KS also have oral lesions
 - Hard palate most common location > gingiva, tongue

Presentation

- Multiple reddish to purple macules that progress to plaques or nodules
- Advanced lesions may cause bleeding, pain, and ulceration

Laboratory Tests

- KSHV can be detected in peripheral blood and saliva

Treatment

- Surgical approaches
 - Surgery limited to cases with significant lesional morbidity
- Drugs

- Regression with HAART
- Small oral lesions: Intralesional vinblastine or cryotherapy

MICROSCOPIC

Histologic Features

- **Patch stage:** Proliferation of small irregularly shaped vascular spaces, which often run parallel to epithelium
 - Slit-like vascular spaces dissect collagen bundles
- **Plaque stage:** Further vascular proliferation along with spindle cell component
 - Intracellular and extracellular hyaline globules
- **Nodular stage:** Unencapsulated infiltrating fascicles of spindled cells with atypia and mitoses
- Lymphangiomatous KS: Boggy or nodular mass
 - Large dilated anastomosing vessels with papillary tufting imparting lymphangioma appearance

ANCILLARY TESTS

Histochemistry

- Hyaline globules are PAS(+), diastase resistant

Immunohistochemistry

- **Positive:** Nuclear HHV8, CD34, CD31, FVIIIIRAg
- Lymphatic-specific markers: D2-40, LYVE-1, VEGFR3, PROX1

DIFFERENTIAL DIAGNOSIS

Pyogenic Granuloma

- Lobular, endothelial growth pattern, HHV8(-)

Kaposiform Hemangioendothelioma

- **Positive:** VEGFR3, CD34, CD31; **negative:** FVIIIIRAg, HHV8

Angiosarcoma

- Marked pleomorphism, mitoses, necrosis; **negative:** HHV8

Spindle Cell Squamous Carcinoma

- **Positive:** Epithelial markers; **negative:** HHV8

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Clinical Forms of Kaposi Sarcoma

Type	Risk Group	Sites of Involvement	Clinical Course
Classic	> 70% elderly men; Slavic, Jewish, Italian	Skin of lower extremities	Indolent
Endemic (African)	Children and middle-aged men	Skin of extremities; visceral involvement common; lymphadenopathic type common in children	Indolent in adults; aggressive in children
Iatrogenic/transplantation-associated	Solid organ transplant (0.5% of renal transplant patients); immunosuppressive therapy	Skin of extremities; may have visceral involvement	Variable; may resolve upon cessation of immunosuppressives
AIDS related	HIV(+) patients; more common in homosexual and bisexual men at younger age than classic KS	Skin of head and neck, extremities, genitals; mucosa of upper aerodigestive tract; lymph nodes	Aggressive

KS = Kaposi sarcoma.

KEY FACTS

TERMINOLOGY

- Tumors secondarily involving oral mucosa and jaws that originate from, but are not in continuity with, primary malignancies of other anatomic sites

CLINICAL ISSUES

- ~ 1% of oral malignancies
- Gnathic bone more frequently involved than soft tissue (2:1)
 - Mandible >> maxilla (4:1)
- Attached gingiva most common soft tissue location accounting for > 50% of cases

MICROSCOPIC

- Most common metastatic tumors to oral cavity in **males**: Lung, kidney, prostate
- Most common metastatic tumors to oral cavity in **females**: Breast, genital organs, kidney

- Other primary sites include skin, liver, thyroid, stomach, esophagus, bladder
- Metastatic sarcomas to oral cavity are rare




ANCILLARY TESTS

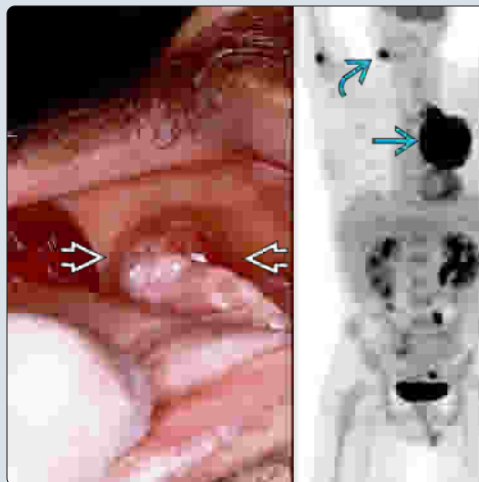
- Markers specific to suspected primary tumor site are indicated, particularly when oral cavity is initial presentation of malignancy

TOP DIFFERENTIAL DIAGNOSES

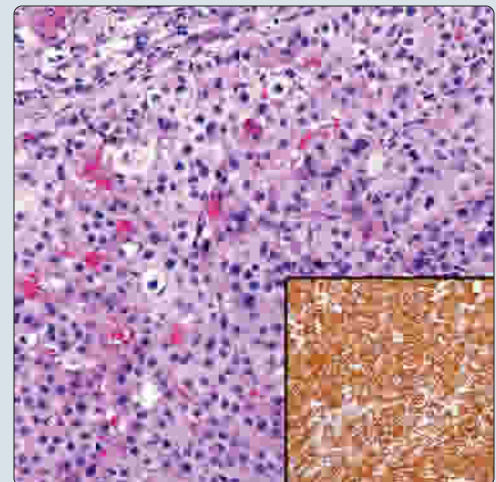
- Immunohistochemistry, clinical history, and radiographic imaging helpful
- Poorly differentiated tumors of both soft tissue and bone may need to be distinguished from metastases
- Both soft tissue and intraosseous high-grade salivary gland carcinomas can share histologic features of metastatic tumors
- Clear cell renal cell carcinoma shares features with intraosseous clear cell carcinoma

Metastatic Lung Carcinoma to Mandible


(Left) A 55-year-old man with a soft tissue mass  growing out of a recent extraction socket as the initial presentation of lung cancer is shown. PET showed a 10-cm lung mass  and bone metastases to the humerus and mandible . (Right) Biopsy of a mandibular mass demonstrates an adenocarcinoma with marked pleomorphism and numerous mitoses. Immunohistochemistry is helpful in confirming the metastatic origin of the tumor, including CK7 (inset) among others.



Immunohistochemistry Required When Evaluating Metastases

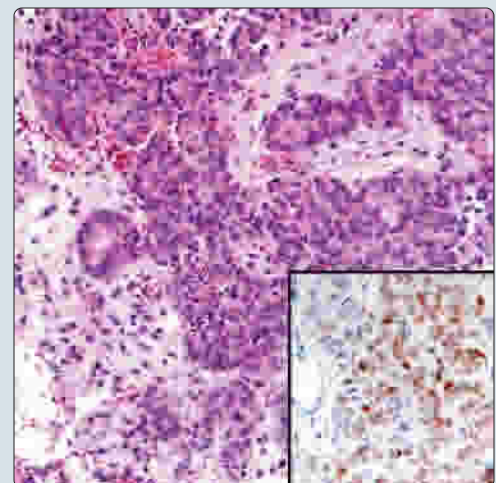


MR of Metastatic Disease to Jaw

(Left) An 85-year-old woman who presented with a 3-month history of jaw pain is shown. A large destructive mass  is noted on this T1WI MR in the retromolar trigone at the proximal ramus, showing bone involvement. (Right) The patient had a history of endometrial adenocarcinoma, and a biopsy of the retromolar mass showed a metastatic tumor consistent with that diagnosis. The tumor was positive for ER (inset) and PR receptors. The genital organs account for ~ 15% of metastases to gnathic bone in females.



Metastatic Endometrial Carcinoma to Jaw



TERMINOLOGY**Definitions**

- Tumors secondarily involving oral mucosa and jaws that originate from, but are not in continuity with, primary malignancies of other anatomic sites
 - Lymphomas and leukemias are excluded by definition

ETIOLOGY/PATHOGENESIS**Pathogenesis**

- Metastases involve various complex signaling pathways, including epithelial to mesenchymal transition, angiogenesis, growth factors, and inhibition of apoptosis

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Rare: ~ 1% of oral malignancies
- Age
 - 5th-7th decades
- Sex
 - Bone: Equal gender distribution
 - Soft tissue: Male > female (2:1)

Site

- **Bone**
 - Gnathic bone more frequently involved than soft tissue (2:1)
 - Mandible >> maxilla (4:1)
- **Soft tissue**
 - Attached gingiva most common location: > 50% of cases
 - Tongue 2nd most common site: ~ 25% of cases

Presentation

- Gnathic bone location
 - Rapid pain, swelling, and loose teeth
 - Nonhealing extraction site
 - Presumed that metastases were present prior to extraction and may have been underlying etiology
 - Numb-chin syndrome: Loss of sensation to lower lip and chin due to involvement of inferior alveolar nerve
 - Nonspecific: May be seen in inflammatory processes or primary jaw lesions also
- Soft tissue location
 - Gingival metastases can resemble reactive process, such as pyogenic granuloma
 - Hemorrhage
 - Submucosal mass

Natural History

- ~ 20-25% of metastases to oral cavity represent initial presentation of malignant disease
- Oral cavity may also be 1st sign of malignant disease

Treatment

- Surgical approaches
 - Surgery generally reserved for palliation
 - If oral metastases are isolated, local resection is sometimes advocated
- Adjuvant therapy
 - Treatment usually palliative and to improve quality of life

Radiation

- Palliative measure, used to control widespread disease

Prognosis

- Poor; average survival: 7 months

MICROSCOPIC**Histologic Features**

- Metastatic tumor should be histologically similar to primary site of origin
- Metastases to **gnathic bone**
 - **Male:** Lung (22%), prostate (11%), renal (9%), adrenal (8%)
 - **Female:** Breast (41%), adrenal (8%), genital organs (8%), renal (7%)
- Metastases to **soft tissue**
 - **Male:** Lung (33%), renal (14%), colorectal (5%)
 - **Female:** Breast (25%), genital organs (15%), renal (12%), lung (9%)
- Other primary sites include skin, liver, thyroid, stomach, esophagus, bladder
- Adenocarcinoma most frequent tumor type
- Metastatic sarcomas to oral cavity are rare

ANCILLARY TESTS**Immunohistochemistry**

- Markers specific/unique to suspected primary tumor site are indicated, particularly when oral cavity is initial presentation of malignancy

DIFFERENTIAL DIAGNOSIS**Primary Tumor**

- Immunohistochemistry, clinical history, and imaging helpful
 - When exuberant tissue growth appears in postextraction site, metastases should be considered
- Poorly differentiated tumors of both soft tissue and bones may need to be distinguished from metastases
- Both soft tissue and intraosseous high-grade salivary gland carcinomas can share histologic features of metastatic tumors
 - Breast carcinoma vs. salivary duct carcinoma, mammary analogue secretory carcinoma
- Clear cell renal cell carcinoma shares features with intraosseous clear cell carcinoma
- When metastases represents initial presentation, PET scans may be indicated

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3. Divya KS et al: Numb chin syndrome: a case series and discussion. *Br Dent J.* 208(4):157-60, 2010
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5. Hirshberg A et al: Metastatic tumours to the oral cavity - pathogenesis and analysis of 673 cases. *Oral Oncol.* 44(8):743-52, 2008

PRIMARY TUMOR**Specimen**

- Excisional biopsy; resection including
- Glossectomy, mandibulectomy, maxillectomy, palatectomy
- Neck (lymph node) dissection
- Specimen type/tumor site
 - Vermilion border upper lip; vermillion border lower lip; mucosa of upper lip; mucosa of lower lip anterior floor of mouth; floor of mouth, NOS
 - Lateral border of tongue; ventral surface of tongue, not otherwise specified (NOS); dorsal surface of tongue, NOS; anterior 2/3 of tongue, NOS
 - Commissure of lip upper gingiva (gum); lower gingiva (gum)
 - Hard palate; buccal mucosa (inner cheek); vestibule of mouth (upper; lower); alveolar process (upper; lower); mandible; maxilla
- Tumor laterality: Left, right, midline
- Tumor focality: Single focus, multifocal
- Tumor size: Greatest dimension in centimeters

Histologic Type

- Squamous cell carcinoma (SCC), conventional
- Variants of SCC
- Carcinomas of minor salivary glands
- Adenocarcinoma, non-salivary gland type
 - Adenocarcinoma, NOS (low, intermediate, high grade)
- Neuroendocrine carcinoma
- Mucosal melanoma

Histologic Grade

- Well- (G1), moderately (G2), and poorly differentiated (G3)
- Salivary gland carcinomas are separated into low, intermediate, and high grade

Invasion

- Lymph-vascular invasion; perineural invasion
- Margin assessment: Uninvolved or involved by invasive carcinoma or high-grade (moderate or severe) dysplasia (include distance in mm and location per orientation)

REGIONAL LYMPH NODES**Cervical Lymph Nodes: Unilateral or Bilateral**

- Separated into pN0 (no regional node metastasis), pN1, pN2(a-c), pN3 based on number and size of involved node(s)
 - pN1: Single ipsilateral lymph node ≤ 3 cm
 - pN2: Single ipsilateral lymph node > 3 cm ≤ 6 cm (pN2a) or in multiple ipsilateral lymph nodes < 6 cm (pN2b) or in bilateral or contralateral nodes < 6 cm (pN2c)
 - pN3: Metastasis in a lymph node > 6 cm

PROGNOSTIC GROUPS**For All Carcinomas Excluding Mucosal Melanoma**

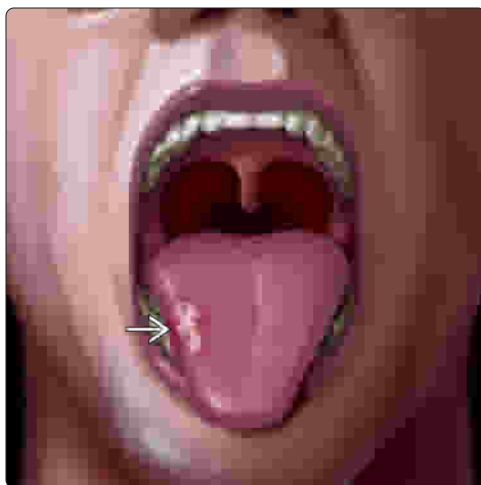
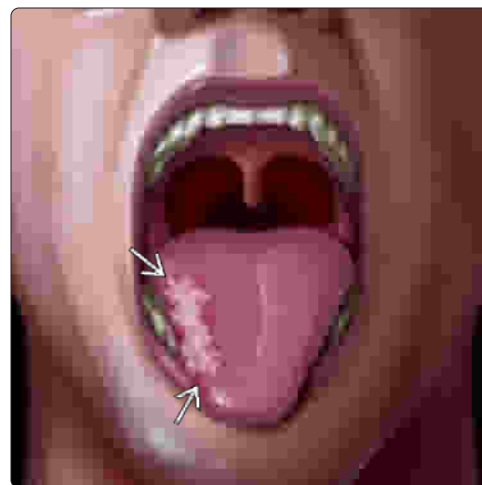
- pTis: Carcinoma in situ
- pT1: Tumor 2 cm or less in greatest dimension
- pT2: Tumor > 2 cm but < 4 cm in greatest dimension
- pT3: Tumor more than 4 cm in greatest dimension
- pT4a: Moderately advanced local disease.
 - Lip: Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, e.g., chin or nose
 - Oral cavity: Tumor invades adjacent structures only (e.g., through cortical bone [mandible, maxilla], into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)
- pT4b: Very advanced local disease; tumor invades masticator space, pterygoid plates, or skull base, &/or encases internal carotid artery

For Mucosal Melanoma

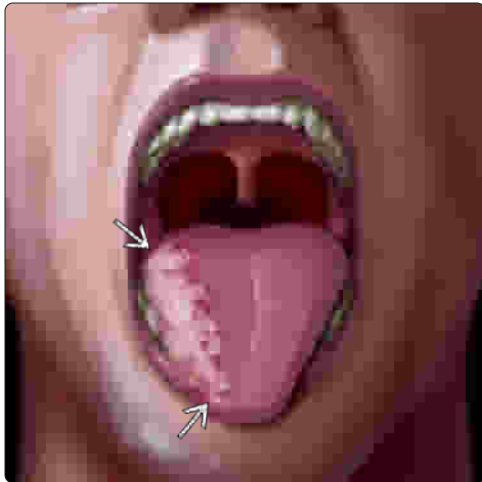
- pT3: Mucosal disease
- pT4a: Moderately advanced disease; tumor involving deep soft tissue, cartilage, bone, or overlying skin
- pT4b: Very advanced disease; tumor involving brain, dura, skull base, lower cranial nerves (IX-XII), masticator space, carotid artery, prevertebral space, or mediastinal structures
- pN1: Regional lymph node metastases present
- pM1: Distant metastasis present

T1 Oral Tongue Carcinoma

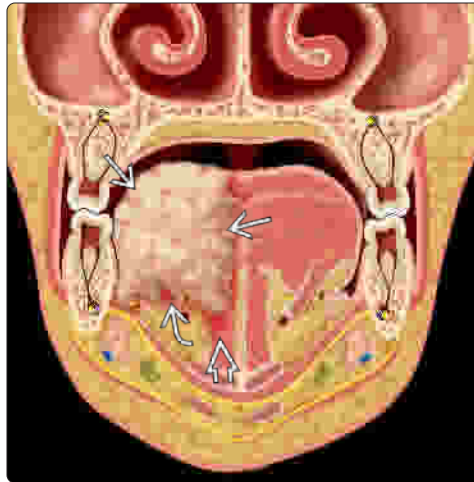
(Left) Graphic illustrates a small dorsolateral oral tongue squamous cell carcinoma ➡, which is ≤ 2 cm and is staged as a T1 oral cavity tumor. The oral tongue is described as having lateral, dorsal, and ventral surfaces. Ventral refers to the undersurface of the tongue. (Right) Graphic illustrates a larger primary squamous cell carcinoma of the lateral aspect of the oral tongue ➡. The carcinoma measured > 2 cm but ≤ 4 cm, qualifying as a T2 oral cavity cancer.

**T2 Oral Tongue Carcinoma**

T3 Oral Tongue Carcinoma

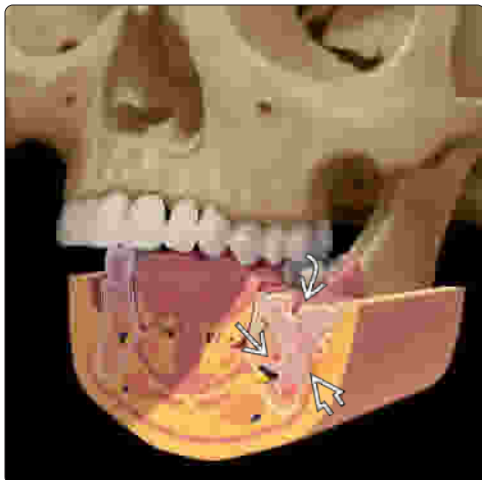


T4a Oral Tongue Carcinoma

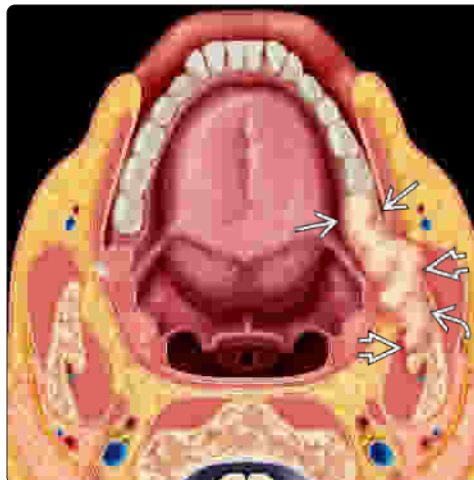


(Left) Graphic illustrates an even larger carcinoma measuring > 4 cm and staged as a T3 squamous cell carcinoma. Preoperative imaging is important with large lesions to determine whether there is any deep extension, which would then stage this as a T4 squamous cell carcinoma. (Right) Coronal graphic illustrates an oral tongue squamous cell carcinoma invading the deep tongue musculature, genioglossus, and hyoglossus. Deep muscle invasion designates T4a tumor.

T4a Oral Cavity Carcinoma

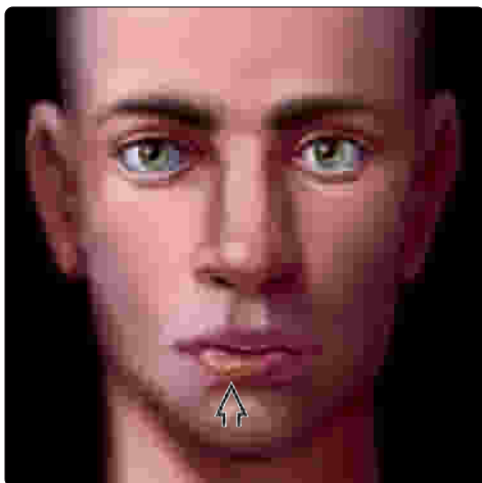


T4b Oral Cavity Carcinoma

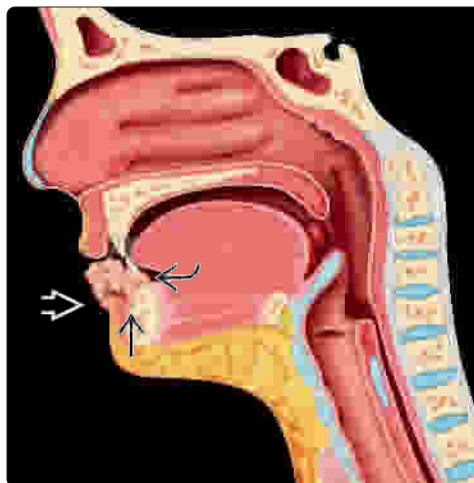


(Left) Graphic demonstrates a SCC arising from mucosa overlying the alveolar ridge & extending to the lower gingivobuccal sulcus & onto the buccal mucosa. There is invasion into the mandibular marrow, which designates this as T4a oral cavity tumor. (Right) Squamous cell carcinoma arising from retromolar gingiva & extending to the mandible & masticator space is shown. Masticator space, pterygoid plate, skull base, &/or carotid artery encasement determine T4b staging.

pT2 Lip Cancer



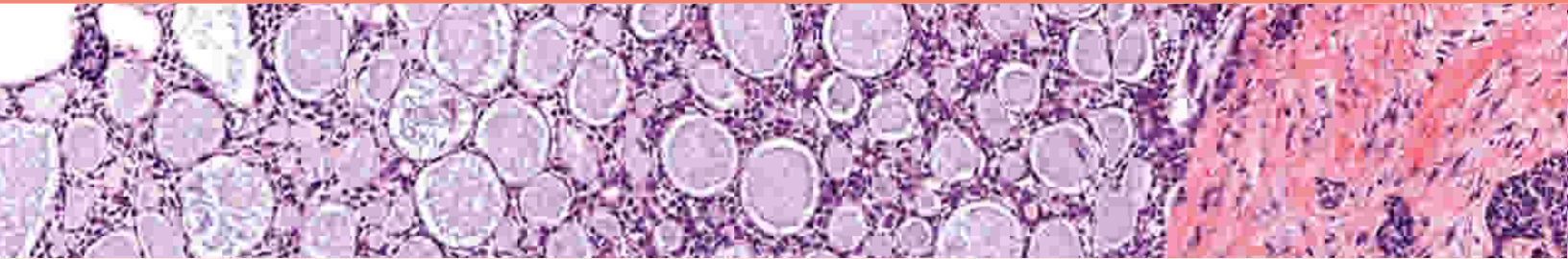
pT4a Lip Cancer



(Left) pT2 lip cancer includes tumors measuring > 2 cm but < 4 cm in greatest dimension. pT1 lip cancers measure < 2 cm, and pT3 lip cancers measure > 4 cm in greatest dimension. (Right) Depiction of a pT4a lip cancer represents moderately advanced local disease with tumor invading through cortical bone, floor of mouth, or skin of face (e.g., chin). pT4a cancer also includes invasion of inferior alveolar nerve (not shown).

SECTION 5

Salivary Glands



Major Salivary Glands	444
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Major Salivary Glands

MACROSCOPIC ANATOMY

Major Glands

- Major salivary glands include paired parotid, submandibular (submaxillary), and sublingual glands
 - Surrounded by delicate fibrous capsule with intraglandular septa dividing them into lobules
- Parotid glands** (15-30 g), largest, are located subcutaneously anterior to ear and are divided by facial nerve into superficial and deep lobes
 - Superficial lobe larger, flat, & quadrangular; deep lobe wedge-shaped & extends into parapharyngeal space
 - Main (Stensen) duct (~ 7 cm) traverses through masseter and buccinator muscles and drains to oral cavity opposite 2nd maxillary molar
 - Only gland with intraparenchymal lymph nodes
- Submandibular glands** (~ 10 g) are located in deep posterior floor of mouth adjacent to mandible
 - Main (Wharton) duct (~ 5 cm) traverses floor of mouth and drains to oral cavity at sublingual caruncle, just lateral to frenulum
- Sublingual glands** (2-4 g) are located in anterior floor of mouth adjacent to mandible
 - Main (Bartholin) duct drains into submandibular duct near its termination
 - Numerous small (Rivinus) ducts drain directly to floor of mouth along plica sublingualis

MICROSCOPIC ANATOMY

Acini and Ducts

- Salivary functional unit (salivon) consists of acinus and draining duct system
- Acini can be serous, mucous, or mixed, and composition can be used to distinguish major salivary glands
 - Parotid is purely serous; submandibular is mixed, serous predominant; sublingual is mixed, mucous predominant
 - Serous acini are spherical with pyramid-shaped cells containing large basophilic zymogen granules
 - Mucous acini are more tubular with round cells containing sialomucin granules






- Mixed acini consist of mucous acini with crescent-shaped caps of serous cells (serous demilunes)
- Acinar lumina drain into branching duct system that modifies saliva and delivers it to oral cavity
- Intercalated ducts** are intralobular, between acini and striated ducts
 - Lined by single layer of cuboidal cells
 - Longest in parotid, shorter in submandibular, and very short in sublingual gland
- Striated ducts** are intralobular and deliver saliva to larger excretory ducts
 - Lined by columnar cells with eosinophilic cytoplasm and parallel striations at basal aspect
 - Striations represent basal membrane invaginations with numerous mitochondria and play role in modifying saliva
 - Longest in submandibular, shorter in parotid, and very short in sublingual gland
- Interlobular** and main **excretory ducts** are located in interlobular septa and outside gland, respectively
 - Lined by pseudostratified columnar epithelium with rare goblet cells; become stratified and squamous near their termination in oral cavity
- Contractile myoepithelial cells are flat cells with numerous cytoplasmic processes (basket cells) that aid in propagating secretions
 - Present between epithelial cells and basal lamina in acini, intercalated ducts, and proximal striated ducts
- Noncontractile basal cells are present in striated and excretory ducts
- Parotid parenchyma contains abundant mature adipose tissue; submandibular gland has less
 - Large branches of facial nerve are seen in parotid interlobular septa
- Rare sebaceous cells may be seen in parotid gland and submandibular ducts

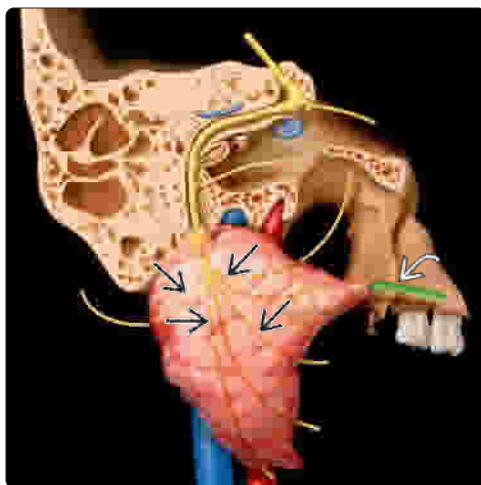
VARIATIONS

Age-Related

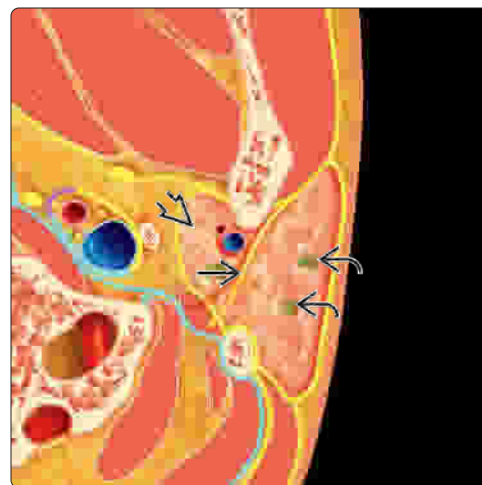
- Atrophy and oncocytic metaplasia are more common with age

Graphic of Nerves in Parotid Gland

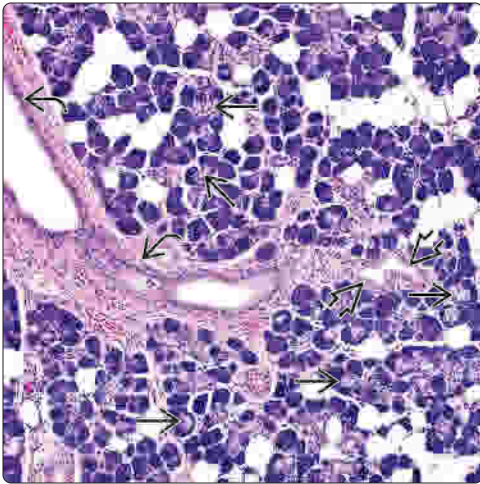
(Left) Branches of the facial nerve  artificially divide the quadrangular superficial parotid lobe from the deep lobe. The main duct  drains into the oral cavity opposite the 2nd maxillary molar. (Right) The deep parotid lobe  is wedge-shaped and extends into the parapharyngeal space. Note the intraparotid lymph nodes  and the facial nerve branch  separating the deep lobe from the superficial lobe.



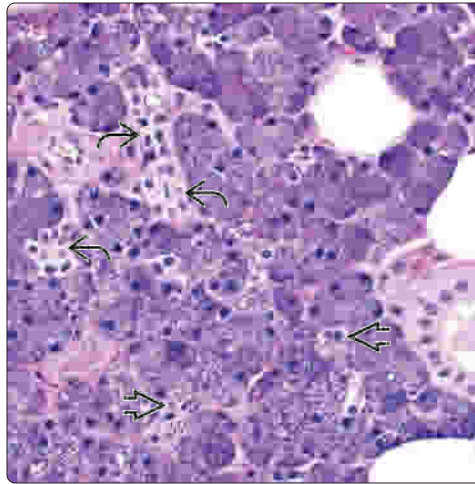
Graphic of Parotid Gland Anatomy



Parotid Excretory Ducts

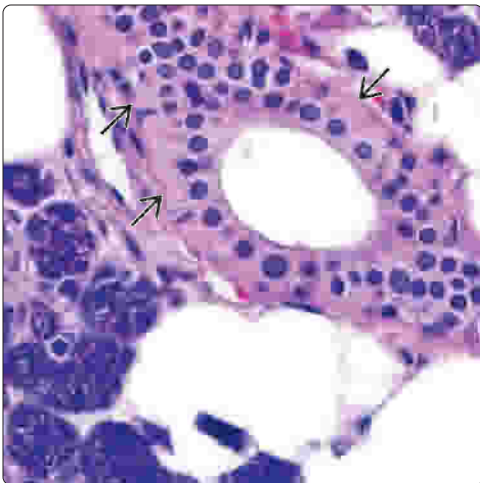


Parotid Intercalated Ducts

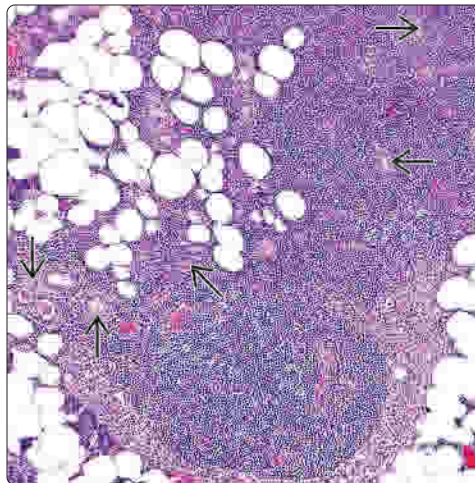


(Left) Intercalated ducts receive secretions from acini and are easily recognizable in parotid glands. They deliver secretions to intralobular striated ducts, which drain to progressively larger intralobar and interlobar excretory ducts. (Right) Intercalated ducts are lined by simple cuboidal epithelium with pale cytoplasm. Some intercalated duct cells may contain residual zymogen granules.

Parotid Striated Duct

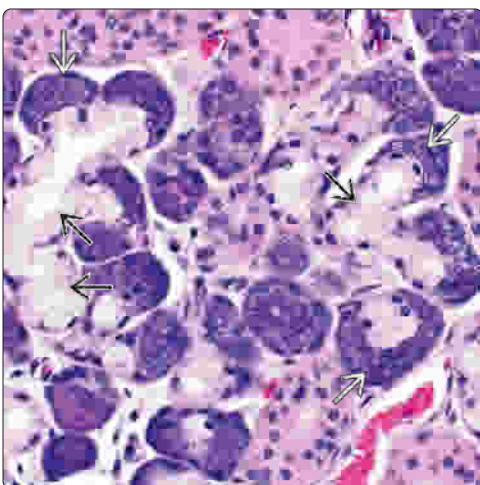


Intraparotid Lymph Node

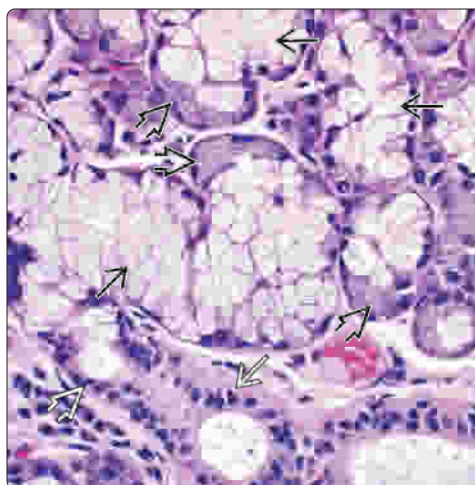


(Left) Striated ducts are intralobular ducts, lined by columnar cells with eosinophilic cytoplasm and round central nuclei. Invaginations of the basal cell membrane yield striations seen in histologic sections. The cells have numerous mitochondria, which cause the cytoplasmic eosinophilia. (Right) Late embryologic encapsulation accounts for up to 30 intraparotid lymph nodes, often containing salivary gland inclusions that represent 1st echelon drainage for malignancies of the face, scalp, and ear.

Serous Demilunes



Sublingual Acini



(Left) Serous demilunes consist of tubular mucous acini capped by a crescent-shaped collection of serous cells. These have been shown to be an artifact of fixation. (Right) The sublingual gland is mixed, with a predominance of tubular mucous acini, many of which are capped by serous acini. They have very short intercalated ducts that communicate with short striated ducts.

Polycystic Disease of Parotid Gland

KEY FACTS

TERMINOLOGY

- Marked dilation and cystic change within intercalated ducts of parotid gland

CLINICAL ISSUES

- Female >>> male
- Recurrent, fluctuating bilateral parotid gland swelling
- Not associated with polycystic disease of other organ systems
- Swelling not related to eating

IMAGING

- Bilateral, uniform, generalized post-contrast enhancement, reflecting multiple parenchymal cysts
- Main parotid duct is uninvolved

MICROSCOPIC

- Salivary gland lobules are enlarged by multifocal to diffuse cystic dilation of intercalated ducts
- Lobular architecture is maintained

- Cysts are irregularly sized and may be discreet or interconnected
- Epithelial lining of variable morphology
- Lumens may also contain proteinaceous, eosinophilic material, with variable inspissation


ANCILLARY TESTS

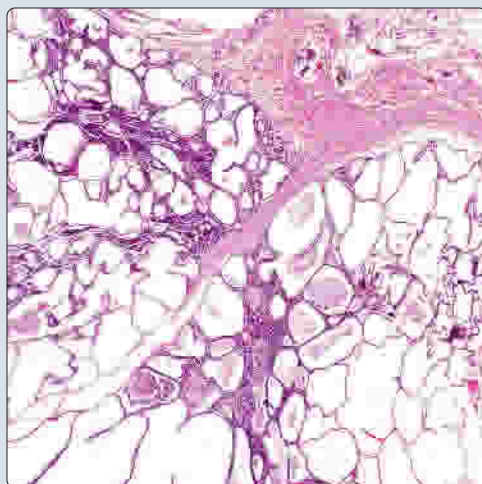
- **Cytology**
 - Low cellularity with minimal proteinaceous background
 - Scattered epithelial cell clusters, individual epithelial cells, red blood cells, and histiocytes
 - Lack of lymphoid cell component

TOP DIFFERENTIAL DIAGNOSES

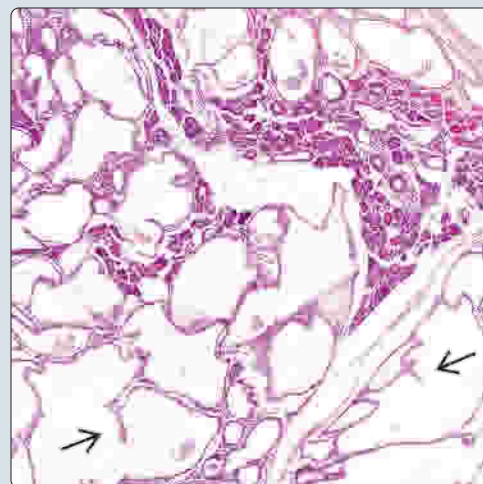
- **Cystic salivary gland neoplasms**
 - Mucoepidermoid carcinoma or cystadenocarcinoma
- **Sialodochiectasis or chronic sialiectasis**
 - Duct dilatation or pooling of contrast in weakened ducts
- **Sclerosing polycystic adenosis**

Normal Tissue Replaced by Cysts




(Left) Low-power view shows polycystic disease of the parotid. The normal parenchyma of the parotid gland is replaced by variably sized cystic structures. Note the preservation of the lobular architecture. **(Right)** Cystic dilation of the ductal structures intimately associated with residual normal serous acini. Note the individual finger-like protrusions of the septal wall extending into the cystic lumina . The amount of residual functional parenchyma varies.



Serous Acini Surrounded by Dilated Cysts

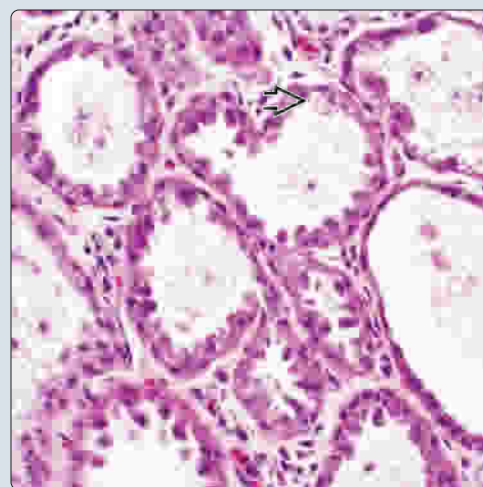


Dilated Intercalated Ducts

(Left) Medium-power image demonstrates residual serous acini, 2 striated ducts , and dilated intercalated ducts . Note that the striated ducts are not involved in the cystic process. The dilated cysts are lined by a flattened epithelial layer. **(Right)** Apocrine-like cytomorphology may be evident within the cystic epithelial lining with an eosinophilic cytoplasm. The nuclei are round and bland in appearance. Microvesicular cytoplasmic vacuolation  is common in polycystic disease of the parotid (PDP). Mitotic activity is inconspicuous.



Apocrine Change in Cyst Lining



TERMINOLOGY

Synonyms

- Dysgenetic polycystic parotid gland disease

Definitions

- Marked dilation and cystic change within intercalated ducts of parotid gland
 - Striated and excretory ducts unaffected

ETIOLOGY/PATHOGENESIS

Inherited or Familial

- Might be sex linked (85% in females)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare developmental anomaly
 - Not associated with polycystic disease of other organ systems
- Age
 - Typically becomes evident in childhood
 - However, overt clinical appearance may be delayed into adulthood
- Sex
 - Female >>> male

Presentation

- Recurrent, fluctuating bilateral parotid gland swelling
- May be present for years prior to diagnosis
- Swelling not related to eating
- Typically not painful

Treatment

- Biopsy or excision only for diagnosis or cosmesis

Prognosis

- No malignant transformation
- No association with other cystic degenerative diseases

IMAGING

Radiographic Findings

- Bilateral, uniform, generalized post-contrast enhancement, reflecting multiple parenchymal cysts
- Main parotid duct is uninvolved
- MRI shows uniformly decreased T1 signal and uniformly increased T2 signal

MACROSCOPIC

General Features

- Exaggerated lobularity of glandular subcapsular surface
- Cut section may display mottled yellow nodules of spongy consistency

MICROSCOPIC

Histologic Features

- Salivary gland lobules are enlarged by multifocal to diffuse cystic dilation of intercalated ducts
 - Lobular architecture is maintained

- Possible thickening of fibrous septa
- Honeycomb or latticework-like architectural pattern within lobules
- Lobules may be affected to different degree
 - Residual serous acinar structures may be present
- Cysts are irregularly sized and may be discrete or interconnected
 - Epithelial lining of variable morphology
 - Flattened and attenuated, cuboidal to apocrine-like
 - Polygonal with microvesicular cytoplasmic vacuolation
 - Vesicular, vacuolated epithelial cells may be sloughed into cystic lumens
 - Short, finger-like epithelial septations may extend into lumen
 - Cysts may display direct communication with normal-appearing serous acini or striated ducts
 - In keeping with dilation of intercalated ducts
- Lumens may also contain proteinaceous, eosinophilic material, with variable inspissation
 - Secretions display variable morphology
 - Amorphous; Sialolith-like with concentric laminations; crystalline and star-like with radiating projections
 - Luminal material may be reactive with Congo-Red and show apple-green birefringence under polarized light
 - Consistent with amyloid
- Minimal to absent inflammatory changes

ANCILLARY TESTS

Cytology

- Low cellularity with minimal proteinaceous background
- Scattered epithelial cell clusters, individual epithelial cells, red blood cells, and histiocytes
 - Polygonal epithelial cells with moderate cytoplasm
 - Nuclei round with small to inconspicuous nucleoli
 - Cytoplasm homogeneous to vacuolated
- Lack of lymphoid cell component

DIFFERENTIAL DIAGNOSIS

Cystic Salivary Gland Neoplasms

- Mucoepidermoid carcinoma or cystadenocarcinoma
- Not bilateral, multilobular, or with maintained lobular architecture

Sialodochiectasis or Chronic Sialectasis

- Duct dilatation or pooling of contrast in weakened ducts

Sclerosing Polycystic Adenosis

- Circumscribed, prominent sclerosis, hyperplastic epithelial proliferation, including solid lobules, often with prominent eosinophilic granules

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KEY FACTS

TERMINOLOGY

- HIV salivary gland disease (HIV SGD) includes HIV infected individuals with xerostomia, enlargement of 1 or more major salivary glands, or both

ETIOLOGY/PATHOGENESIS

- Caused by HIV infection

CLINICAL ISSUES

- Salivary gland involvement typically occurs in early stages of HIV disease prior to development of AIDS
- Primarily adult men aged 20-60 years
- Salivary gland involvement almost always parotid gland (98%)
 - Much less often submandibular gland (2%)
- Bilateral involvement in ~ 60% of cases
- Serology evaluation will confirm HIV positivity

- Highly active antiretroviral treatment (HAART) shown to reduce size of parotid swellings and even result in regression of HIV SGD
- Successful outcome using HAART is reflected by diminution in viral load and immune restoration

MICROSCOPIC

- Florid follicular hyperplasia with attenuated to absent mantle lymphocytes; disruption of germinal centers (follicle lysis); presence of multinucleated giant cells (MGCs) localized to inter- and intrafollicular areas, adjacent to or within epithelial component; monocytoïd B cells can be found in clusters
- Multiple squamous epithelial-lined cysts and lymphoepithelial islands present typically permeated by lymphocytes &/or monocytoïd B cells

ANCILLARY TESTS

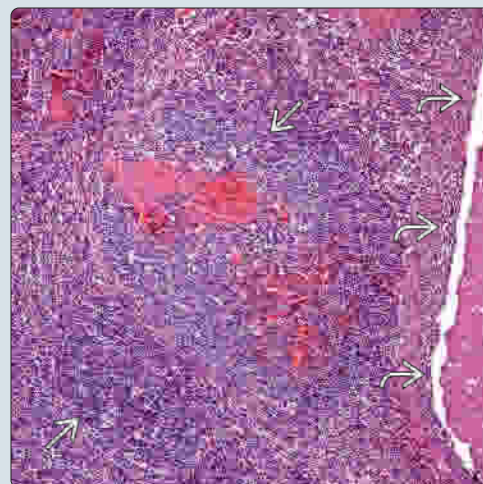
- HIV p24 core antigen immunoreactivity found in germinal centers (follicular dendritic cells), MGCs

HIV Salivary Gland Disease

(Left) H&E shows intraparotid multicystic lesion in which the cysts prove to be lined by benign epithelium & presence of enlarged, irregularly shaped lymphoid follicles within the wall of the cyst. Residual parotid gland parenchyma is present outside the cystic lesion. (Right) In the wall of the cyst, there are irregularly shaped lymphoid follicles with attenuated to absent mantle lymphocytes & follicle lysis. The cyst is lined by epithelium, which is obscured secondary to permeation by lymphocytes &/or monocytoïd B cells.

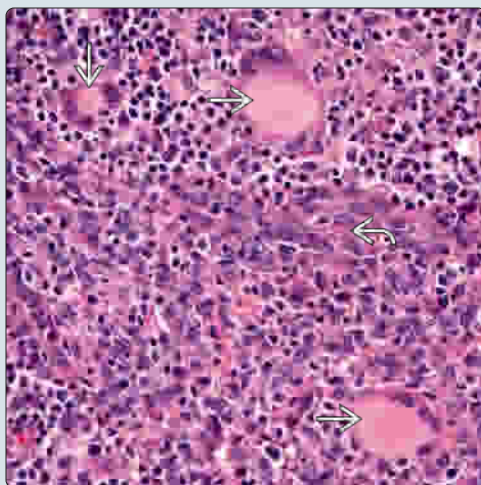


HIV Salivary Gland Disease

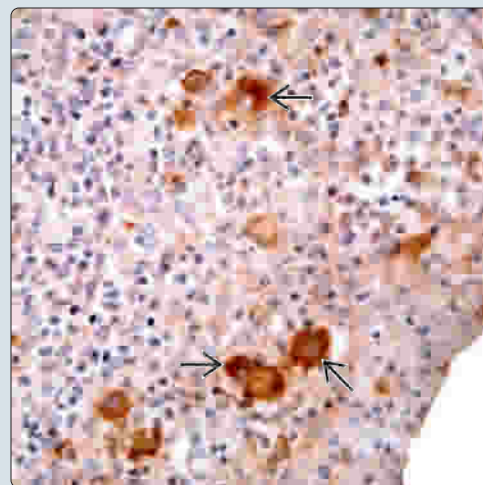


HIV Salivary Gland Disease

(Left) Multinucleated giant cells, localized adjacent to epithelium but present also in inter- and intrafollicular areas, in combination with follicular hyperplasia are features suggesting a diagnosis of HIV SGD. (Right) The multinucleated giant cells are immunoreactive with HIV p24 core antigen. In conjunction with the clinical history, presence of cystic lesions in 1 or more salivary glands, light microscopic features, and HIV p24 immunoreactivity, the diagnosis of HIV SGD is established.



HIV Salivary Gland Disease



TERMINOLOGY**Abbreviations**

- HIV salivary gland disease (HIV SGD)

Definitions

- HIV SGD includes HIV-infected individuals with xerostomia, enlargement of 1 or more major salivary glands, or both

ETIOLOGY/PATHOGENESIS**Infectious Agents**

- Caused by HIV infection

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Exact incidence of salivary gland enlargement in HIV-infected individuals not known
- Age
 - Primarily adult men aged 20-60 years
 - May occur in babies born from HIV-infected mothers
- Sex
 - Male >>> female (9:1)
 - Equal gender distribution for babies of HIV-infected mothers

Site

- Salivary gland involvement almost always parotid gland (98%)
 - Much less often submandibular gland (2%)
- Bilateral involvement in ~ 60% of cases

Presentation

- Symptoms include painless swelling of 1 or more salivary glands, xerostomia, dry eyes, arthralgias
- Salivary gland involvement typically occurs in early stages of HIV disease prior to development of AIDS
- Sjögren syndrome-like illness also identified in AIDS patients

Laboratory Tests

- Serology evaluation will confirm HIV positivity

Treatment

- Options, risks, complications
 - Treatment options for HIV SGD vary, including surgical resection (parotidectomy, conservative excision, curettage), radiation, and symptomatic relief
- Drugs
 - Highly active antiretroviral treatment (HAART) shown to reduce size of parotid swellings and even result in regression of HIV SGD

Prognosis

- Parotid gland involvement does not appear to play any role in course of disease or progression to AIDS
- Successful outcome using HAART is reflected by diminution in viral load and immune restoration

IMAGING**Radiographic Findings**

- CT scan and MR show unilateral or bilateral multicentric cysts of varying sizes

MICROSCOPIC**Histologic Features**

- Similar to changes seen in lymph nodes with early to chronic phases, including
 - Florid follicular hyperplasia with attenuated to absent mantle lymphocytes; disruption of germinal centers (follicle lysis); presence of multinucleated giant cells (MGCs) localized to inter- and intrafollicular areas, adjacent to or within epithelial component; monocytoid B cells can be found in clusters
- Multiple squamous epithelial-lined cysts and lymphoepithelial islands present typically permeated by lymphocytes &/or monocytoid B cells

ANCILLARY TESTS**Cytology**

- Heterogeneous lymphoid population; presence of foamy macrophages and MGCs

Immunohistochemistry

- Lymphoid component reactive for B- and T-cell markers
- Epithelial markers delineate epithelial-lined cysts and lymphoepithelial islands
- HIV p24 core antigen immunoreactivity found in germinal centers (follicular dendritic cells), MGCs

DIFFERENTIAL DIAGNOSIS**Infectious Disease**

- Combination of cystic epithelial proliferation, MGCs, and lymphoid component not typically seen in infectious diseases other than HIV SGD

Lymphoepithelial Cyst

- Cystic epithelial proliferation similar to HIV SGD but lacks alterations of lymphoid follicles/germinal centers and absence of MGCs; absence of p24

Cystic Salivary Gland Neoplasms

- Differentiation from salivary gland neoplasms (benign and malignant) straightforward, as cellular components diagnostic for a given cystic salivary gland neoplasm are absent in HIV SGD

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IgG4-Related Salivary Gland Disease

KEY FACTS

TERMINOLOGY

- Chronic fibroinflammatory salivary gland disease with characteristic morphology included within spectrum of systemic IgG4-related diseases

ETIOLOGY/PATHOGENESIS

- Recognized as autoimmune-mediated disease

CLINICAL ISSUES

- Primarily affects submandibular gland
- Pain and swelling of affected gland common; often associated with ingestion of food
- May be localized to salivary glands or may be associated with sclerosing lesions in extrasalivary gland tissues (i.e., systemic IgG4-related disease)
- Excellent response to steroid (e.g., glucocorticoids, rituximab)

MICROSCOPIC

- Preservation of lobular architecture

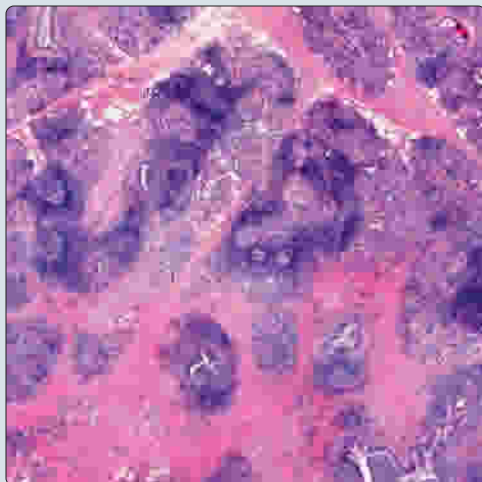
- Lobules are separated by fibrosis
- Storiform-type fibrosis seen in other organs may not be present in salivary glands
- Dense lymphoplasmacytic infiltrate within lobules and extended into fibrosis, including
 - Sheets of mature plasma cells and florid lymphoid hyperplasia
- Phlebitis may or may not be identified

ANCILLARY TESTS

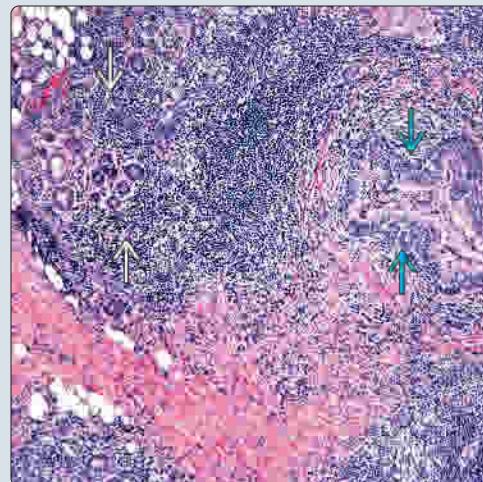
- IgG4 immunostaining essential test for pathological diagnosis of IgG4-related disease
 - For salivary glands > 100 per HPF in conjunction with light microscopic features considered highly suggestive for diagnosis
- IgG4(+)/IgG(+) plasma cell ratio more powerful tool than IgG4(+) plasma cell counts in establishing diagnosis
 - IgG4(+)/IgG(+) plasma cell ratio of > 40% considered cutoff value in any organ

Lobular Architecture

(Left) At low magnification, there is fibrosis with retention of the lobular architecture and dense inflammatory infiltrate including reactive lymphoid hyperplasia and the presence of acinar atrophy. (Right) The dense inflammatory infiltrate is present around ducts and within the lobules, the latter characterized by acinar atrophy. The inflammatory component also involves perilobular fibrotic bands.

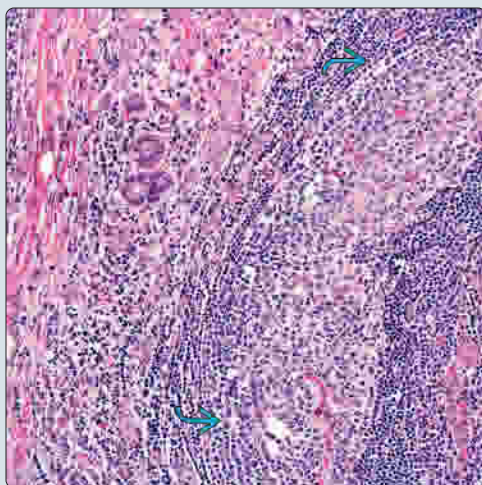


Perilobular Fibrosis

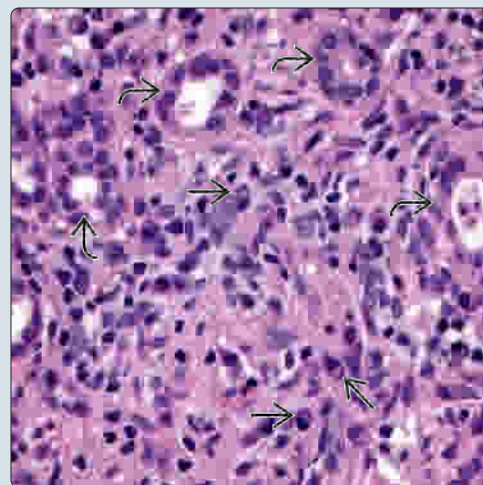


Inflammatory Cell Infiltrate

(Left) Lymphoplasmacytic infiltrate is shown within the lobules and extended into fibrosis. A prominent germinal center is present. (Right) At higher magnification, the inflammatory cell infiltrate includes mature lymphocytes and mature plasma cells, the latter characterized by the presence of perinuclear "hof" representing the Golgi apparatus. Residual acini are present, but there is marked atrophy.



Lymphoplasmacytic Cells



TERMINOLOGY

Synonyms

- Chronic sclerosing sialadenitis (CSS)
 - Küttner tumor
 - Punctate parotitis
- Mikulicz disease (MD)
 - Was considered to be subtype of Sjögren syndrome (SS) based on histopathological similarities
 - Recent studies indicate that patients with MD show high serum IgG4 concentration
 - MD considered IgG4-related disease distinguishable from SS

Definitions

- Chronic fibroinflammatory salivary gland disease with characteristic morphology included within spectrum of systemic IgG4-related diseases, including
 - Autoimmune pancreatitis and involvement of extrapancreatic organs (e.g., kidney, lung, retroperitoneum, liver, gallbladder, lymph nodes, breast, salivary glands, lacrimal glands, aorta)

ETIOLOGY/PATHOGENESIS

Immune Mediated

- Recognized as autoimmune-mediated disease

Obstructive Sialadenitis

- Prior to IgG4 association, sialolithiasis felt to be commonly associated with CSS of submandibular gland
 - May be true in percentage of non-IgG4-related cases

CLINICAL ISSUES

Epidemiology

- Incidence
 - Unknown
- Age
 - Most often occurs in 4th to 7th decades
- Sex
 - Affects males slightly more often than females

Site

- Primarily affects submandibular gland
 - Typically, 1 gland and rarely multiple salivary glands (major and minor) may be affected in single patient

Presentation

- Pain and swelling of affected gland common; often associated with ingestion of food
- Patients may present with asymptomatic swelling of affected gland
- May be localized to salivary glands or may be associated with sclerosing lesions in extrasalivary gland tissues (i.e., systemic IgG4-related disease)

Laboratory Tests

- Serum IgG4, IgG, IgG4/IgG ratio (normally 3-6%) typically elevated
- Antibodies present in Sjögren syndrome, including anti-SS-A, anti-SS-B not found in CSS

- Absence of antineutrophilic antibodies (cytoplasmic and perinuclear)
- Eosinophilia, hypergammaglobulinemia, and antinuclear antibodies (ANA) may be present in systemic but not localized disease

Treatment

- Options, risks, complications
 - IgG4-related sialadenitis is steroid sensitive
- Surgical approaches
 - CSS associated with sialolithiasis
 - Removal of stone by surgery, endoscopy, or lithotripsy
 - In ~ 20% of cases, symptoms persist, necessitating surgical resection of involved gland

Prognosis

- Excellent response to steroid (e.g., glucocorticoids, rituximab)
 - Rituximab-induced B-cell depletion in IgG4-RD leads to rapid clinical and histological improvement accompanied by swift declines in serum IgG4 concentrations
- Rarely, extranodal marginal zone B-cell lymphoma (MALT) of salivary gland and salivary duct carcinoma may arise in background of CSS

MICROSCOPIC

Histologic Features

- Well-defined to circumscribed lesion involving variable proportion of gland or entire gland characterized by
 - Preservation of lobular architecture
 - Lobules are separated by fibrosis
 - Thickening of interlobular septa by sclerotic tissue
 - Storiform-type fibrosis seen in other organs (e.g., pancreas) may not be as frequently present in salivary glands
 - Dense lymphoplasmacytic infiltrate within lobules and extended into fibrosis including
 - Sheets of mature plasma cells
 - Large irregular lymphoid follicles with expanded germinal centers (follicular lymphoid hyperplasia)
 - Acinar atrophy
 - Phlebitis (obliterative or nonobliterative) may or may not be identified
 - Obliterative phlebitis may or may not be present
 - Venous channels are obliterated by dense lymphoplasmacytic infiltrate, but this finding is not as frequently seen as in other organ sites (e.g., pancreas)
 - Not required for diagnosis
- Metaplastic changes of ducts may be present, including squamous &/or mucous metaplasia
- Noncaseating granulomas may be seen
 - Likely result of mucus extravasation from ducts in cases associated with sialolithiasis

ANCILLARY TESTS

Immunohistochemistry

- IgG4 immunostaining essential test for pathological diagnosis of IgG4-related disease

- Appropriate cutoff number of IgG4(+) plasma cells varies per organ and for salivary and lacrimal glands > 100 per HPF in conjunction with light microscopic features considered highly suggestive for diagnosis
- Abundant IgG4-bearing plasma cells virtually always present in inflamed lobules, interlobular septa, and occasionally in germinal centers
- Strongly recommended, even in straightforward cases, as simple, highly reproducible test providing strong confirmatory evidence for diagnosis
- IgG4(+) plasma cell count alone may not help to distinguish between IgG4-related disease and disorders that are not part of that disease spectrum
- IgG4(+)/IgG(+) plasma cell ratio more powerful tool than IgG4(+) plasma cell counts in establishing diagnosis
 - IgG4(+)/IgG(+) plasma cell ratio on immunostaining widely used to assess preferential shift to IgG4 production in affected sites
 - IgG4(+)/IgG(+) plasma cell ratio of > 40% considered cutoff value in any organ
 - In absence of other corroborative findings, IgG4(+)/IgG(+) plasma cell ratio of > 40% in and of itself is not considered sufficient pathological evidence of IgG4-related disease
 - Non-IgG4-related disease entities can have IgG4(+)/IgG(+) plasma cell ratios of > 40%, including but not limited to multicentric Castleman disease, rheumatoid arthritis
- Plasma cells
 - CD138(+)
 - Polytypic kappa and lambda light chain by immunohistochemistry &/or in situ hybridization
- CD3(+) interfollicular T cells present, especially in association with ducts and acini
- CD20(+) B cells mostly restricted to lymphoid follicles
- Follicles express Bcl-6 and are **negative** for Bcl-2

Genetic Testing

- Immunoglobulin heavy chain includes polyclonal rearrangement in majority of cases

DIFFERENTIAL DIAGNOSIS

Chronic Sialadenitis, Not Otherwise Specified

- Lacks presence of increased IgG4 plasma cells
- May be associated with sialolithiasis

Sialolithiasis

- Caused by calcareous concretions within salivary gland ducts &/or parenchyma as result of mineralization of debris accumulated within duct lumina
- Calculi particularly common in submandibular gland (Wharton duct) accounting for 80-90% of cases
 - Parotid gland (Stensen duct) involvement in 10-20% of cases
- Radiographic analysis represents most reliable means to detect presence of calculi
- Microscopic features include
 - Calculi seen in parenchyma or ducts
 - With time, parenchymal changes include fibrosis, parenchymal atrophy with loss of acini, chronic inflammation, ductal dilatation, scarring

- May share histologic features with IgG4 CSS, but lacks uniform presence of increased IgG4 plasma cells

Sarcoidosis of Salivary Glands

- Most often involves parotid gland as isolated process or as part of syndrome termed uveoparotid fever (Heerfordt disease) characterized by
 - Parotitis, xerostomia, uveitis, and facial nerve palsy
- Presence of noncaseating granulomatous inflammation

Sjögren Syndrome

- Typically, disease of parotid gland that rarely presents as submandibular gland disease
- Lacks interlobular fibrosis, dense lymphoplasmacytic cell infiltrate with (IgG4[+]) plasma cells

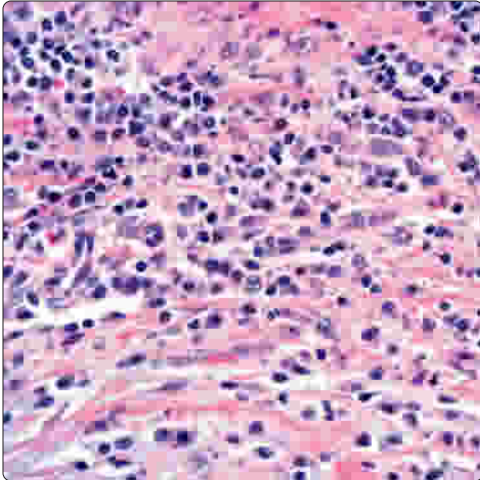
Lymphoepithelial Sialadenitis (LESA)

- Typically, disease of parotid gland that rarely presents as submandibular gland disease
- Lacks interlobular fibrosis, dense lymphoplasmacytic cell infiltrate with (IgG4[+]) plasma cells

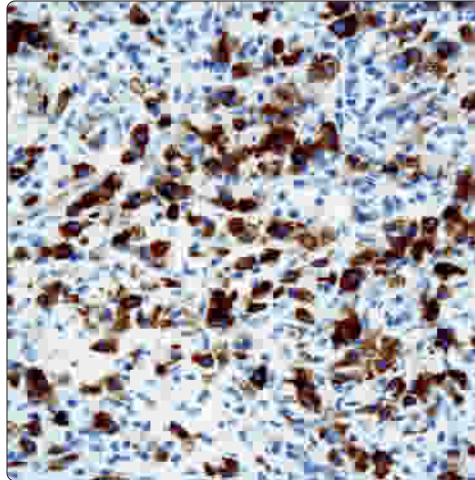
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Numerous Plasma Cells

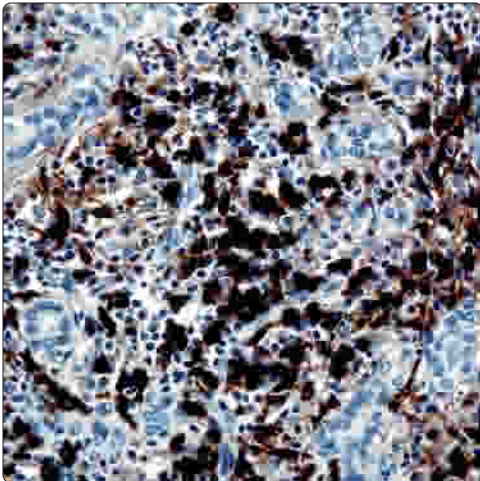


CD138 Expression

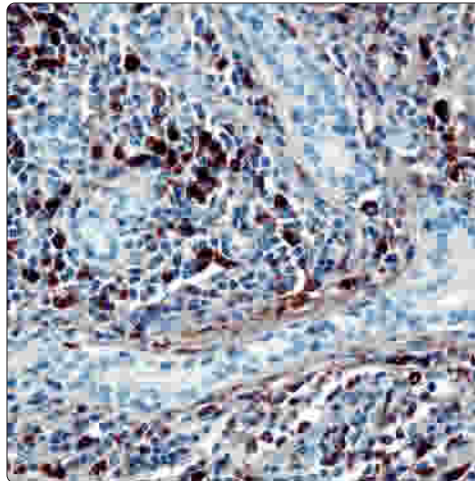


(Left) In addition to infiltrating the salivary gland lobules, the lymphoplasmacytic cell infiltration also permeates into the perilobular fibrotic bands. Mature plasma cells represent the dominant inflammatory cell type. (Right) Immunohistochemical staining of the plasma cells includes CD138 reactivity. There is also polytypic kappa and lambda light chain by immunohistochemistry &/or in situ hybridization (not shown).

IgG4-Positive Plasma Cells

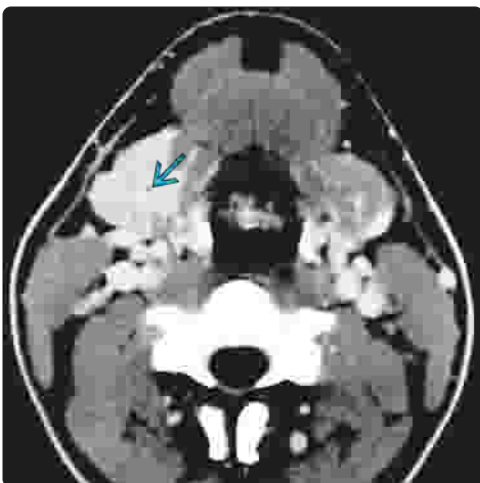


IgG4-Positive Plasma Cells

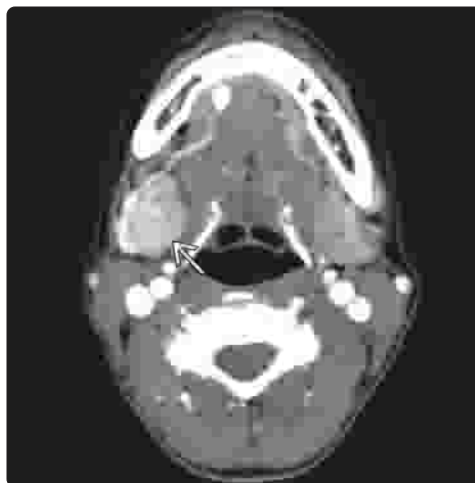


(Left) Immunohistochemical staining of the plasma cells shows an increase in the number of IgG4(+) plasma cells. Abundant IgG4-bearing plasma cells are virtually always present. (Right) IHC staining of the plasma cells also includes IgG(+) plasma cells. The IgG4(+)/IgG(+) plasma cell ratio is > 40%, and in conjunction with the light microscopic pathologic findings, is confirmatory of the diagnosis. IgG4(+)/IgG(+) plasma cell ratio is a more powerful tool than IgG4(+) plasma cell counts in establishing the diagnosis.

Sialadenitis and Chronic Sclerosing Sialadenitis



Sialadenitis and Chronic Sclerosing Sialadenitis



(Left) Chronic sclerosing sialadenitis may result 2° to sialolithiasis. Asymmetric enhancement of the right enlarged submandibular gland is seen. Note slight dilatation of the submandibular duct hilum [blue arrow]. (Right) Axial CECT shows an enhancing, enlarged right submandibular gland [black arrow] secondary to a stone in the distal duct at the level of the ductal papilla. Histologically, evidence of stone formation was present with secondary chronic sclerosing sialadenitis (not shown).

Benign Lymphoepithelial Cyst

KEY FACTS

TERMINOLOGY

- Benign cystic epithelial lesion intimately associated with lymphocytic proliferation within cyst wall

CLINICAL ISSUES

- Practically all salivary lymphoepithelial cysts are found within parotid gland
- Average age of presentation: 5th-6th decades
- Usually asymptomatic
- Usually has compressible, unilateral swelling
- Surgical excision treatment of choice
- BLECs are not known to recur

MICROSCOPIC

- Unilocular and unicystic lesion that is typically well demarcated within parotid gland
- Ordinarily lined by stratified squamous epithelium, although cuboidal, columnar, or pseudostratified epithelial types may occasionally be seen

- Lymphoid component, to include germinal center formation, is dense and found within wall of cyst

ANCILLARY TESTS

- CD4:CD8 ratio normal

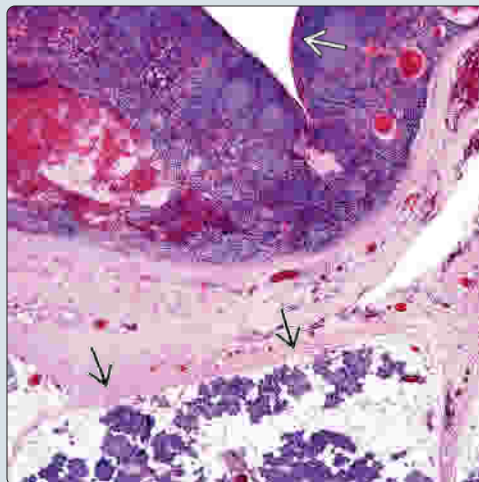
TOP DIFFERENTIAL DIAGNOSES

- HIV-associated salivary gland disease**
 - HIV-associated cystic lesions are typically multiple, possibly bilateral, and also contain lymphoepithelial islands
- Cystic squamous cell carcinoma**
 - Lymph node architecture, with cyst lined by ribbon of atypical epithelium, including mitotic figures and keratinaceous debris
- Warthin tumor**
 - Papillae are lined with bilayered, oncocytic epithelium
- Mucoepidermoid carcinoma**
 - BLECs lack solid epidermoid nests, intermediate cells, or infiltrative architectural pattern of MEC

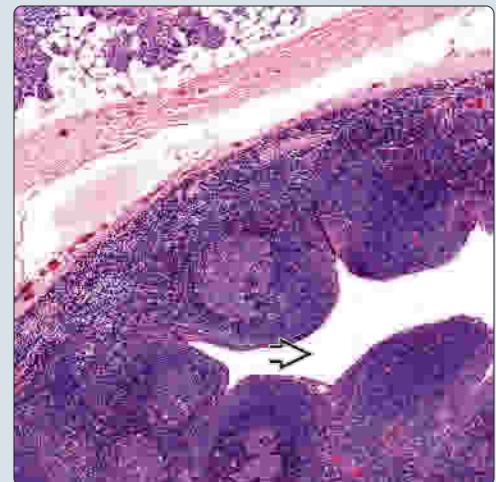
Fibrous Tissue Between Cyst and Normal

(Left) There is a well-demarcated junction between the lymphoid population and the fibrous connective tissue separating the cyst from the normal salivary gland. The epithelium lines the cyst.

(Right) This benign lymphoepithelial cyst (BLEC) of the parotid gland has a corrugated architectural pattern due to the germinal center formations. The lumen of the cyst shows an empty space.

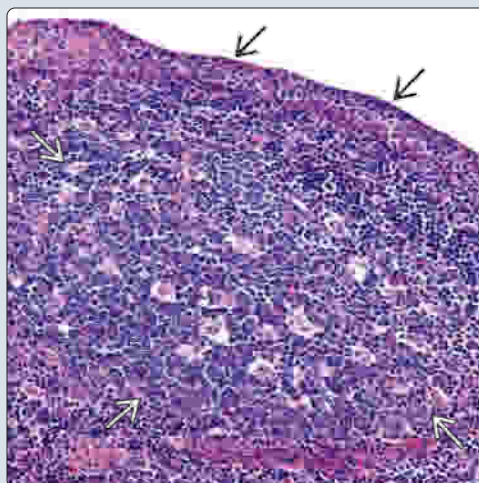


Corrugated Architectural Pattern

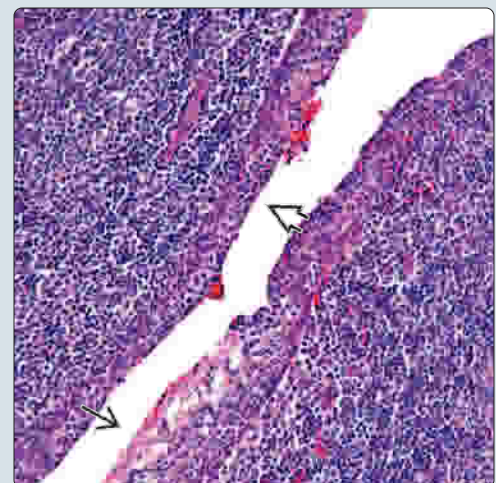


Germinal Center Formation

(Left) Medium-power view shows a lymphocytic germinal center underlying the squamous epithelial cystic lining. Unlike BLEC in HIV disease (which has a CD4:CD8 ratio < 1), the CD4:CD8 ratio is normal in this case. (Right) Medium-power view shows squamous epithelial cystic lining of a LEC. A flattened, squamous epithelial lining shows an intimate association with the lymphoid population, a common finding in BLEC. Portions of the epithelium demonstrate an irregular parakeratinized surface.



Squamous Epithelial Lined Cyst



TERMINOLOGY

Abbreviations

- Benign lymphoepithelial cyst (BLEC)

Definitions

- Benign, cystic epithelial lesion intimately associated with lymphocytic proliferation within cyst wall

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Theories attempt to explain dual population of cystic salivary epithelium and distinct lymphoid component
 - Possibly derived from embryologic branchial cleft remnants, representing intraparotid branchial cleft cysts
 - Entrapped salivary epithelium within intraparotid/periparotid lymph node
 - Salivary duct cyst that recruits lymphoid component
 - Akin to tumor-associated lymphoid proliferation (TALP) seen with salivary gland malignancies (e.g., acinic cell carcinoma, mucoepidermoid carcinoma)

Infectious

- If bilateral, there is strong HIV type-1 association

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare
 - Develops in 3-6% of early HIV-infected patients
- Age
 - Occurs over very wide range
 - Mean: 5th-6th decades
- Sex
 - Historically, more common in males
 - Recent studies show BLECs to occur with slightly greater frequency in females

Site

- Nearly all BLECs are found within parotid gland
 - Although histologically similar, intraoral lymphoepithelial cysts are considered of tonsillar origin
- Typically unilateral
 - If bilateral, HIV association should be considered

Presentation

- Usually asymptomatic
- Usually has compressible, unilateral swelling
- Occasional patients complain of tenderness, pain, or facial nerve palsy

Treatment

- Surgical excision treatment of choice

Prognosis

- BLECs are not known to recur

MACROSCOPIC

Size

- Mean: 3 cm

MICROSCOPIC

Histologic Features

- Unilocular and unicystic lesion that is typically well demarcated within parotid gland
- Cysts are ordinarily lined by stratified squamous epithelium
 - Cuboidal, columnar, or pseudostratified epithelium may line cyst
 - Goblet cells, oncocytes, or sebaceous cells may be seen
- Dense lymphoid component within cyst wall
 - Germinal center formation is regularly identified

ANCILLARY TESTS

Immunohistochemistry

- CD4:CD8 ratio normal
 - In HIV-associated cystic lesions, CD4:CD8 ratio < 1

DIFFERENTIAL DIAGNOSIS

HIV-Associated Salivary Gland Disease

- HIV-associated cystic lesions are typically multiple, possibly bilateral, and also contain lymphoepithelial islands
- Germinal centers are larger and more irregular
 - Interfollicular tissue contains numerous plasma cells, neutrophils, histiocytes, and large, irregular mononuclear or multinuclear cells

Cystic Squamous Cell Carcinoma

- Lymph node architecture, with cyst lined by ribbon of atypical epithelium, including mitotic figures and keratinaceous debris

Warthin Tumor

- Cystic epithelial proliferation with papillary infolding and intimate lymphoid component
- Papillae are lined with bilayered, oncocytic epithelium

Mucoepidermoid Carcinoma

- Often has cystic component and possible TALP
- BLECs lack solid epidermoid nests, intermediate cells, or infiltrative architectural pattern of mucoepidermoid carcinoma

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Benign Lymphoepithelial Lesion

KEY FACTS

TERMINOLOGY

- Reactive, focal to diffuse polyclonal lymphoid infiltrate of salivary glands leading to parenchymal atrophy and degeneration of glandular elements into irregular epithelial complexes

CLINICAL ISSUES

- Strong association with Sjögren syndrome (SS)
- Mean: 5th to 6th decades
- Female > male (3:1)
- Vast majority affect parotid gland
- Recurrent, firm, diffuse enlargement or swelling of affected gland ± pain
- Anti-Ro/SS-A; anti-La/SS-B; other rheumatologic markers (ANA, SLE, DS-DNA)
- Potential evolution to extranodal marginal zone B-cell lymphoma

MACROSCOPIC

- Multinodular diffuse enlargement to discrete micronodules



MICROSCOPIC

- Effacement of salivary parenchyma by dense infiltrate of lymphocytes and plasma cells
- Lobular effacement variable, with complete effacement in advanced disease
 - Atrophy of glandular and ductal epithelium
- Formation of "lymphoepithelial complexes" (epimyoepithelial islands)
 - Deposits of extracellular, eosinophilic hyaline material, often within lymphoepithelial complex
- Mixture of polyclonal T and B lymphocytes

TOP DIFFERENTIAL DIAGNOSES

- SS, extranodal marginal zone B-cell lymphoma, tumor-associated lymphoid proliferation, benign lymphoepithelial cyst, metastatic carcinoma, chronic sialadenitis

CT Showing Bilateral Parotid Gland Enlargement


(Left) Axial CT shows bilateral parotid gland enlargement ; a finding that is quite frequent in patients who have benign lymphoepithelial lesions. (Right) There are numerous lymphoid follicles and a heavy chronic inflammatory infiltrate in this parotid gland. The epithelium  is seen in the background as small ducts and acini.

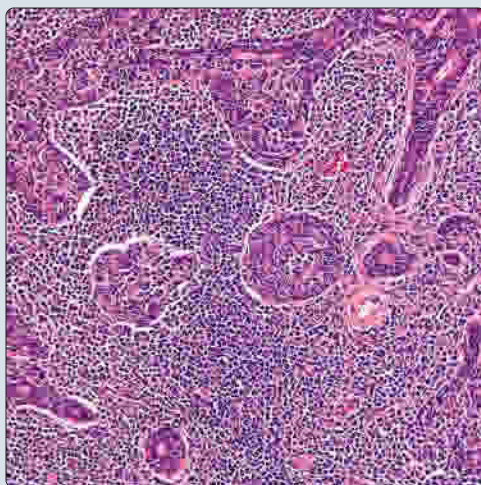


Lymphoid Follicles Within Parotid Tissue

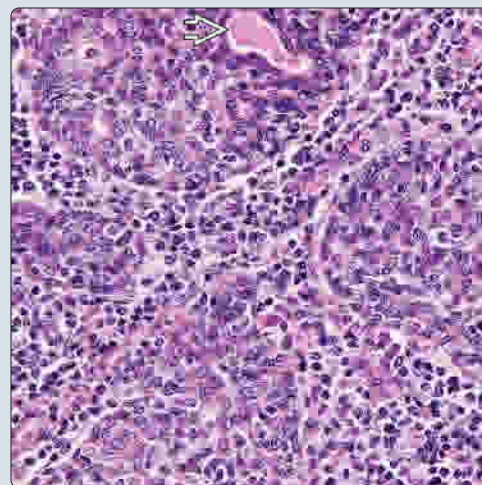


Lymphoepithelial Complexes

(Left) H&E of a parotid gland shows variable effacement of the salivary gland lobules by a chronic inflammatory infiltrate. There are lymphocytes and plasma cells within the epithelium (lymphoepithelial complexes). (Right) Epithelial complexes composed of small, irregular cells with scant cytoplasm display variable infiltration by small lymphocytes. Secretions are focally noted .



Lymphoepithelial Lesion



TERMINOLOGY

Abbreviations

- Benign lymphoepithelial lesion (BLEL)

Synonyms

- Lymphoepithelial sialadenitis
- Myoepithelial sialadenitis

Definitions

- Reactive, focal to diffuse lymphoid infiltrate of salivary glands leading to parenchymal atrophy and degeneration of glandular elements into irregular epithelial complexes

ETIOLOGY/PATHOGENESIS

Association

- Strong association with Sjögren syndrome (SS)
 - Majority of patients with SS also have BLEL of parotid glands (bilateral)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Most cases are associated with SS
 - BLEL occasionally seen independent of SS
 - Usually unilateral, secondary to obstruction
- Age
 - Mean: 5th-6th decades
- Sex
 - Female > male (3:1)

Site

- Vast majority affect parotid gland, commonly bilateral

Presentation

- Recurrent, firm, diffuse enlargement or swelling of affected gland ± pain

Laboratory Tests

- Anti-Ro/SS-A; anti-La/SS-B; other rheumatologic markers (ANA, SLE, DS-DNA)

Treatment

- Excision of affected gland may be required

Prognosis

- Excellent in most cases
- Potential evolution to extranodal marginal zone B-cell lymphoma (EMZBCL), similar to mucosal associated lymphoid tissue lymphomas (MALToma)

MACROSCOPIC

General Features

- Multinodular diffuse enlargement to discrete micronodules

MICROSCOPIC

Histologic Features

- Effacement of salivary parenchyma by dense infiltrate of lymphocytes and plasma cells
 - Lobular architecture preserved with distinct separation of lobules by fibrous septa

- Lobular effacement variable, with complete effacement in advanced disease
- Eosinophils and neutrophils usually absent
- Atrophy of glandular and ductal epithelium
- Formation of "lymphoepithelial complexes" (epimyoeplithelial islands)
 - Complexes of irregular size and morphology
 - Epithelial component composed of small, irregular cells with scant cytoplasm
 - Polygonal or spindled, with indistinct cell borders
 - Variable permeation by B lymphocytes, ranging from small and inconspicuous, to relatively large with clear surrounding halo
- Deposits of extracellular, eosinophilic hyaline material, often within lymphoepithelial complex
- Germinal center formation rare to significant

ANCILLARY TESTS

Cytology

- Cellular smears with mixed inflammatory infiltrate and histiocytes
- Myoepithelial and ductal epithelial cells interspersed with lymphoid infiltrate

Immunohistochemistry

- Mixture of T and B lymphocytes, with polyclonal κ and λ populations

DIFFERENTIAL DIAGNOSIS

Sjögren Syndrome

- BLEL is highly suggestive but not pathognomic of SS
- Ocular and oral signs and symptoms, combined with SS-A/SS-B autoantibodies

Extranodal Marginal Zone B-Cell Lymphoma

- Loss of lobular architecture with destroyed fibrous septa
- Extension beyond gland capsule into adjacent tissues
- Sheets of medium-sized, atypical B cells, destroying epithelium with clonal monocytoid B cells
- Sheets of monoclonal plasma cells (κ or λ light chain restricted)

Tumor-Associated Lymphoid Proliferation

- Secondary lymphoid infiltration associated with salivary malignant neoplasm
- Present at advancing edge or within tumor

Benign Lymphoepithelial Cyst

- Squamous-lined cystic space within lymphoid stroma

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KEY FACTS

TERMINOLOGY

- Reactive, focal to diffuse lymphoid infiltrate of salivary glands leading to parenchymal atrophy and degeneration of glandular elements into irregular epithelial complexes
- **Primary Sjögren syndrome (SS):** Chronic, systemic autoimmune disease primarily affecting parotid and lacrimal glands
- **Secondary SS:** Above in association with another autoimmune disorder

CLINICAL ISSUES

- Mean age: 5th-7th decades
- Female >>> male (9:1)
- Lacrimal and parotid glands most severely affected, commonly bilateral
- Recurrent, firm, diffuse parotid enlargement lasting weeks to months, with occasional remission
 - Typically painless, bilateral swellings of lateral orbital margin

- Diagnosis based upon results of multiple tests
 - Positive anti-SSA (RO) &/or anti-SSB (LA)
 - Rheumatoid factor positive in up to 95%
- Treatment mostly supportive
 - 44x increased risk of developing lymphoma

IMAGING

- MR sialography is best diagnostic study


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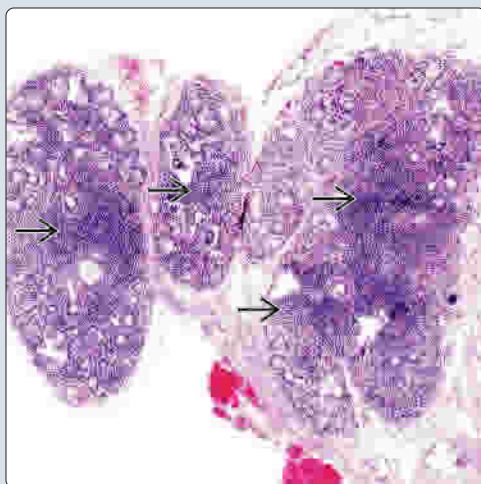
- Minor salivary glands with lymphocytic and plasma cell infiltrate
- Focus score: Number of lymphoid aggregates per 4 mm² of salivary gland tissue
 - Lymphoid aggregate ≥ 50 lymphocytes

TOP DIFFERENTIAL DIAGNOSES

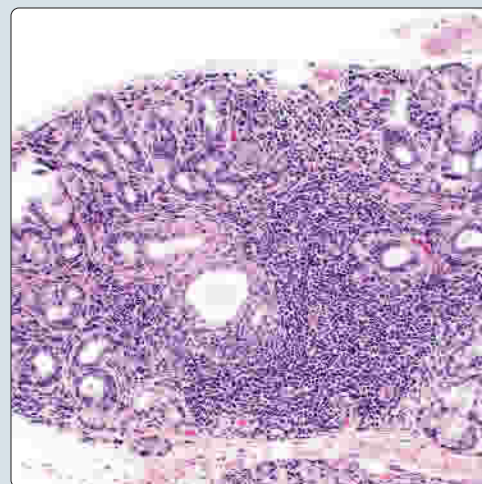
- Benign lymphoepithelial cyst, chronic sialadenitis, tumor-associated lymphoid proliferation (TALP), extranodal marginal zone B-cell lymphoma

4 Foci of Lymphocytes


(Left) Several salivary gland lobules are present in this biopsy. There are at least 4 foci of > 50 lymphocytes aggregated together  in this sample of Sjögren syndrome (SS). These foci are noted within the parenchyma. **(Right)** A focus of > 50 lymphocytes aggregated within the salivary gland parenchyma comprises a focus. There need to be > 1 focus per 4 mm² of salivary gland tissue removed through normal epithelium to qualify as a true focus score.

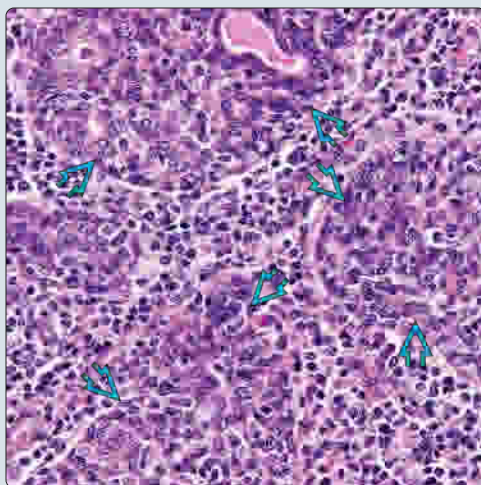


Focus of Lymphocytes

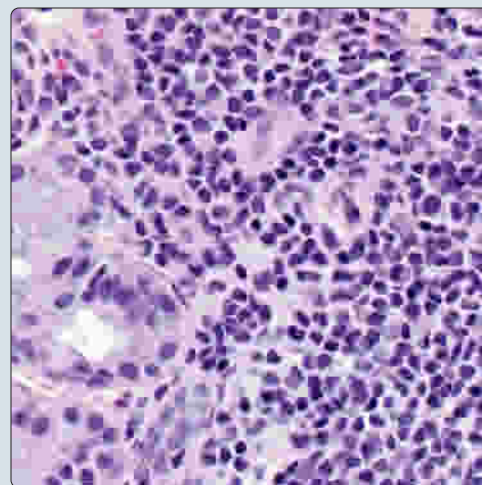


Lymphoepithelial Lesion

(Left) In some cases, there are well-developed lymphoepithelial lesions (epimyoepithelial complexes ) in which there is a mixture of lymphoid elements with the epithelial-myoepithelial islands. Benign lymphoepithelial lesion (BLEL) are seen in most patients with well-developed Sjögren syndrome. **(Right)** The minor salivary glands are immediately adjacent to an aggregate of lymphocytes and plasma cells. Only the lymphocytes are counted in a focus score, although this can be difficult in some cases.



Lymphoid Infiltrate Next to Minor Salivary Glands



TERMINOLOGY

Abbreviations

- Sjögren syndrome (SS)

Definitions

- **Primary SS:** Chronic, systemic autoimmune disease primarily affecting parotid and lacrimal excretory glands, leading to xerostomia and xerophthalmia, respectively
- **Secondary SS:** Above in association with another autoimmune, connective tissue disorder
 - Typically rheumatoid arthritis or systemic lupus erythematosus

ETIOLOGY/PATHOGENESIS

Primary Sjögren Syndrome

- Etiology unknown, yet likely multifactorial and complex

CLINICAL ISSUES

Epidemiology

- Incidence
 - 0.5-3% of population
- Age
 - Mean: 5th-7th decades
 - Peaks at menarche and menopause
- Sex
 - Female >>> male (9:1)
 - Males may be more common in juvenile presentation

Site

- Lacrimal and parotid glands most severely affected
 - Commonly bilateral
- Submandibular, sublingual, and minor salivary glands affected to lesser degree

Presentation

- Fatigue and musculoskeletal pain with dry mouth and dry eyes is classical
- Xerostomia (dry mouth)
 - Taste alterations
 - Difficulties in speech and mastication
 - Possible burning sensation
- Xerophthalmia (dry eyes, keratoconjunctivitis sicca)
 - Pain and foreign body sensation
 - Photosensitivity, ocular fatigue
 - Redness, loss of visual acuity, filamentary keratitis
- Parotid gland
 - Recurrent, firm, diffuse parotid enlargement lasting weeks to months, with occasional remission
 - Possible discomfort/pain, which may increase with eating
- Lacrimal gland
 - Typically painless, bilateral swellings of lateral orbital margin
- Many patients have other connective tissue, autoimmune, or rheumatologic disorders
- Extraglandular manifestations
 - Autoimmune thyroiditis; primary biliary cirrhosis; lung interstitial fibrosis; glomerulonephritis and interstitial nephritis

- Skin with dryness and vasculitis; peripheral neuropathy; carpal tunnel syndrome; dysphagia; reflux; pernicious anemia; arthritis

Laboratory Tests

- Examinations should be performed in sequential order: Anti-SSA antibody, lip biopsy, and parotid gland sialography
- Serology
 - Positive anti-SSA (Ro) &/or anti-SSB (sessile serrated adenoma)
 - Rheumatoid factor positive in up to 95%
 - Antinuclear antibody (ANA) positive in up to 80%
 - Erythrocyte sedimentation rate (ESR) usually elevated
- Salivary flow tests (sialography)

Treatment

- Treatment mostly supportive
- Xerostomia: Adequate hydration and stimulation of salivary flow
- Xerophthalmia
 - Topical: Artificial tears, including eye drops or ointments

Prognosis

- Slowly progressive, evolving over decades, waxing and waning
- Most serious complication is lymphoma development
 - 44x increased risk of developing lymphoma
 - ~ 4-10% of SS patients
 - Typically low grade
 - Extranodal marginal zone B-cell lymphoma (EMZBCL) of mucosa-associated lymphoid tissue (MALT) is most common
 - Represents ~ 85% of lymphomas in SS patients
 - Good prognosis unless transformation into diffuse large B-cell lymphoma
- Juvenile cases may resolve spontaneously at puberty

IMAGING

Radiographic Findings

- Sialography
 - Dilation of ducts (sialodochiectasis) and punctate collections of contrast medium

MACROSCOPIC

General Features

- Overall gland enlargement with intact capsule
- Multinodular to diffuse with or without micronodules

Size

- Variable gland size, although overall enlargement

MICROSCOPIC

Histologic Features

- Major salivary glands with lymphocytic infiltration, acinar atrophy, and formation of epimyoepithelial islands
 - i.e., benign lymphoepithelial lesion
- Labial minor salivary gland biopsy
 - Minor salivary glands with focal lymphocytic infiltration
 - Infiltrate adjacent to normal appearing acini

Revised American-European Consensus Group (AECG) Classification Criteria for Sjögren Syndrome (SS)

Symptom or Test	Result or Interpretation
I: Ocular symptoms (1 of 3)	Daily, persistent troublesome dry eyes for > 3 months Use artificial tear more than 3x per day
II: Oral symptoms (1 of 3)	Daily feeling of dry mouth for > 3 months Recurrent or persistent swollen salivary glands (as adult) Frequently drink liquids to aid in swallowing dry food
III: Ocular tests (1 of 2)	Unanesthetized Schirmer test (≤ 5 mm in 5 minutes) Rose Gengal score or other ocular dye score (≥ 4 according to van Bijsterveld scoring system)
IV: Positive lip biopsy	Focus score of ≥ 1 (lymphocytic aggregate [50+] per 4 mm ² of minor salivary gland tissue obtained through normal-appearing mucosa)
V: Salivary gland tests (1 of 3)	Sialometry: Unstimulated salivary flow ≤ 1.5 mL in 15 minutes Abnormal parotid gland sialography without major duct obstruction Abnormal salivary scintigraphy
VI: Serology	Antibodies to Ro (SSA) or La (SSB) antigens or both
Classification rules for primary SS	Requires any 4 of the 6 criteria, to include either positive lip biopsy or positive serology
Exclusion criteria	Past head and neck radiation treatment; Hepatic C infection; AIDS; preexisting lymphoma; sarcoidosis; graft-vs.-host disease; use of anticholinergic drugs

- Parenchymal acinar atrophy, fibrosis, duct ectasia (chronic sclerosing sialadenitis), or acute inflammation not in keeping with SS
- o Lymphoid aggregate is defined as ≥ 50 lymphocytes
 - Periductal lymphoid aggregates (sialodochitis) not counted
- o Minimum of 4 mm² of minor salivary gland parenchyma required (5-10 minor salivary glands)
- o Focus score: Number of lymphoid aggregates per 4 mm² of salivary gland tissue
 - Focus score of ≥ 1 supportive of SS
 - Correlation increases with greater focus score
- Lacrimal gland with lymphocytic and plasma cell infiltrate

ANCILLARY TESTS

Cytology

- Cellular smears with mixed inflammatory infiltrate and histiocytes
- Myoepithelial and ductal epithelial cells interspersed with lymphoid infiltrate

DIFFERENTIAL DIAGNOSIS

Benign Lymphoepithelial Lesion (BLEL)

- Highly suggestive of SS, especially if bilateral

Benign Lymphoepithelial Cyst

- Benign, cystic epithelial lesion intimately associated with lymphocytic proliferation within cyst wall
- Unilocular and unicystic lesion that is typically well demarcated within parotid gland
- Cysts are ordinarily lined by stratified squamous epithelium
 - o Cuboidal, columnar, or pseudostratified epithelium may line cyst
- Dense lymphoid component within cyst wall

- o Germinal center formation is regularly identified

Chronic Sialadenitis

- Mixed chronic inflammatory infiltrate containing plasma cells, lymphocytes, and neutrophils
- Prominent periductal and acinar fibrosis
- Parenchymal acinar atrophy
- Duct ectasia (sialodochitis) or acute inflammation not in keeping with SS
- Lobular architecture is maintained
- Lack of lymphoepithelial lesions

Tumor-Associated Lymphoid Proliferation

- Secondary lymphoid infiltrate associated with epithelial malignancies
- Present at advancing edge or within tumor

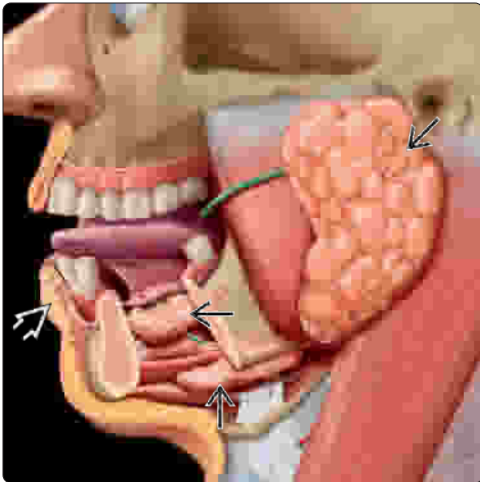
Extranodal Marginal Zone B-Cell Lymphoma

- Loss of lobular architecture with destroyed fibrous septa
- Extension beyond gland capsule into adjacent tissues
- Sheets of medium-sized atypical B cells
 - o Invasion of epithelial complexes by clonal monocytoid B cells
- Sheets of plasma cells

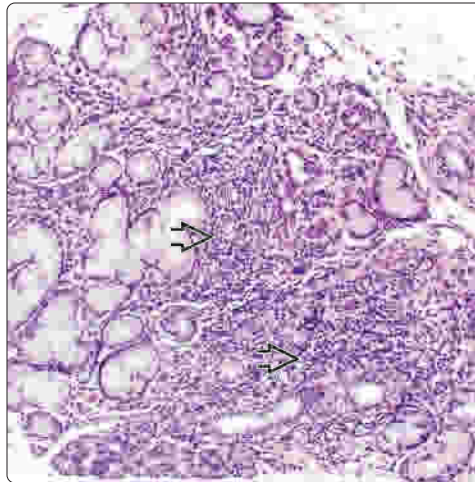
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Increased Salivary Gland Size



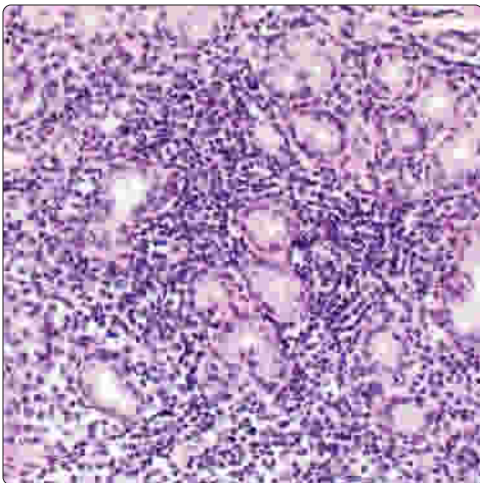
2 Foci of Lymphocytes



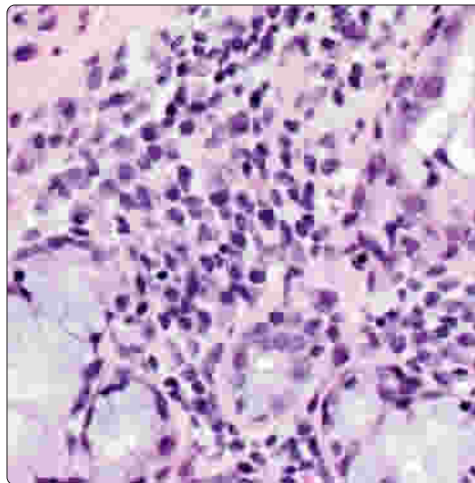
(Left) This graphic demonstrates inflammatory-related enlargement of the major salivary glands [] and minor glands of the lip []. There is still preservation of the lobular architecture.

(Right) There are 2 separate foci [] in these 2 lobules of minor salivary gland. Sometimes separating foci can be challenging, but in general, if there is a fibrous septa or lobular septation, it is counted as a separate focus.

Lymphocyte Aggregate

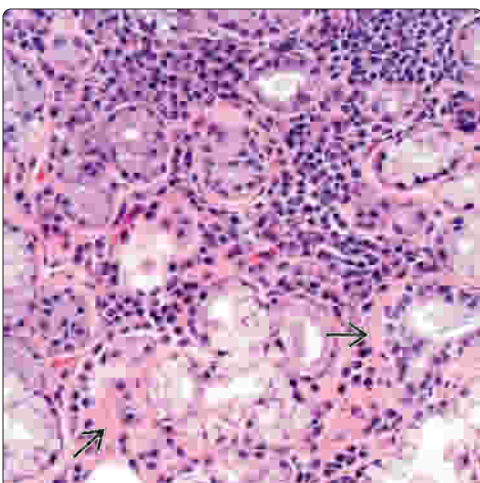


Normal Lymphocytes and Plasma Cells

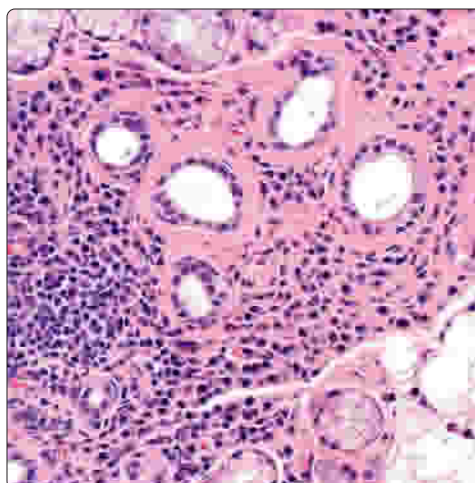


(Left) The salivary gland parenchyma shows infiltration by a collection of lymphocytes. There is no increased fibrosis, no periductal distribution, and no atrophy of the acinar epithelium. These are key features in reaching the diagnosis. **(Right)** The lymphocytes and plasma cells are not atypical. There are no increased mitoses and no pleomorphism. Destructive growth is not appreciated.

Chronic Sialadenitis



Chronic Sclerosing Sialadenitis



(Left) An increased number of plasma cells are seen juxtaposed to the normal, nonatrophic salivary gland parenchyma. There are thin wisps of fibrosis [] but no ectasia or neutrophils. This does not qualify as a focus as the number of lymphocytes is insufficient. **(Right)** In this case of chronic sclerosing sialadenitis, a differential for SS, there is strong periductal and peri-acinar fibrosis, with duct dilatation with a rich inflammatory infiltrate of lymphocytes and plasma cells.

Oncocytosis (Oncocytic Hyperplasia)

KEY FACTS

TERMINOLOGY

- Oncocyte: Altered epithelial cell whose cytoplasm contains vast numbers of abnormal mitochondria
- Oncocytic hyperplasia

ETIOLOGY/PATHOGENESIS

- Oncocytic change associated with normal aging

CLINICAL ISSUES

- Normally seen after 50 years
- May be noted in any salivary gland
- Oncocytic metaplasia and oncocytosis are generally asymptomatic
- No treatment necessary for oncocytic metaplasia
- Nodular oncocytic hyperplasia may present as clinically evident mass

MICROSCOPIC

- Oncocytes are large and polygonal with granular cytoplasm

- Oncocytic metaplasia shows intimate, direct apposition of oncocytic cells with normal salivary gland parenchyma
- Oncocytic hyperplasia may range from small collections to larger, unencapsulated nodules

ANCILLARY TESTS

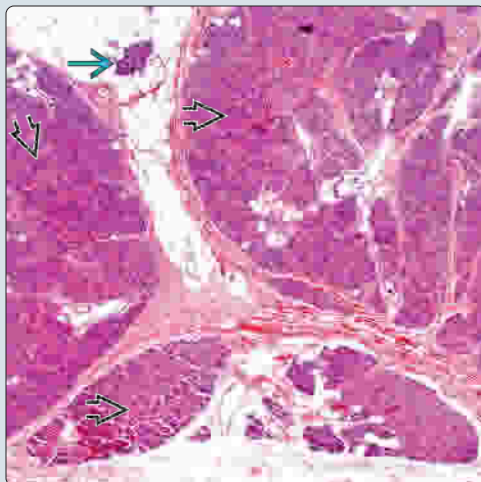
- Phosphotungstic acid hematoxylin (PTAH), Novelli, Luxol fast blue: All highlight mitochondria

TOP DIFFERENTIAL DIAGNOSES

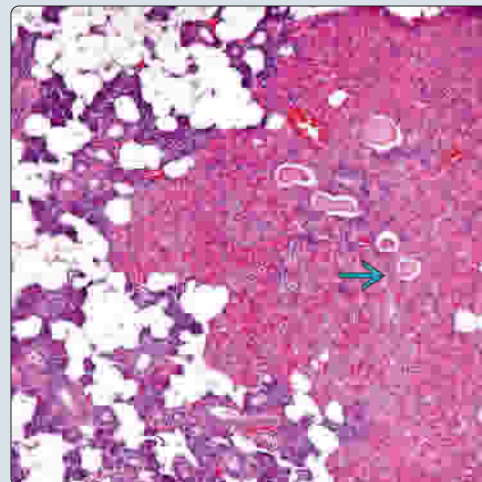
- Oncocytoma
 - Differences between oncocytoma and clinically evident nodular oncocytic hyperplasia are vague
 - Features favoring oncocytoma include partial or full encapsulation, and lack of included ductal structures
- Other salivary gland neoplasms
 - Oncocytic change may be seen in many salivary gland neoplasms
 - Warthin tumor, pleomorphic adenoma, and mucoepidermoid carcinoma

Nodules of Oncocytic Hyperplasia

(Left) Large unencapsulated nodules of oncocytic hyperplasia with scant normal parotid glands are identified. This type of histologic presentation may be correlated to the clinical presentation of a mass. (Right) Oncocytic change may involve the salivary acini, intercalated ducts, and striated ducts. Large, polygonal cells with abundant finely granular eosinophilic cytoplasm are characteristic except in the clear cell variant.

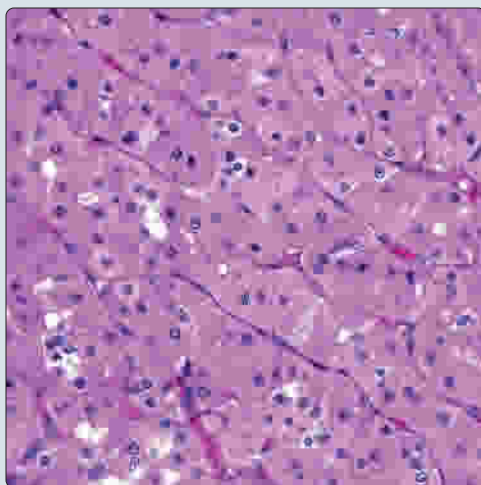


Ducts and Acini Affected by Oncocytosis

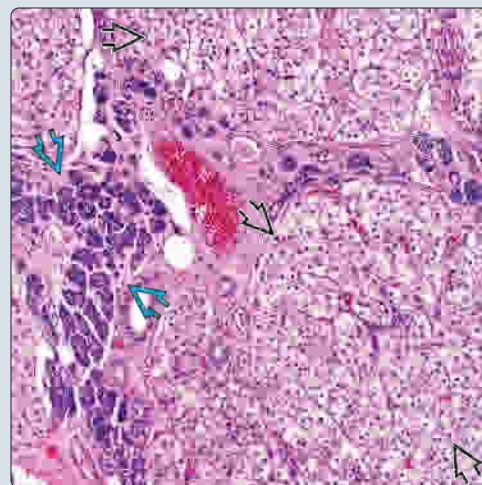


Large Granular Oncocytes

(Left) Oncocytes are characterized by abundant granular eosinophilic cytoplasm, round to oval nuclei, and polygonal morphology. The oncocytic change is due to accumulated mitochondria. (Right) Note the intimate interface between the oncocytic cells (lower right) and the normal parotid gland. In this case, there is clear cell oncocytosis, which is characterized by glycogen accumulation and the peripheralization of the intracytoplasmic mitochondria.



Interface of Oncocytosis With Glandular Acini



KEY FACTS

TERMINOLOGY

- Detached calcified mass within salivary ductal structures or parenchyma
- Formed by accumulation of calcium salts around central focus of bacteria, inspissated mucus, or foreign material
- Detached calcified mass within salivary ductal structures or parenchyma resulting from mineralization of entrapped debris

CLINICAL ISSUES

- Middle-aged adults are most commonly affected
- Symptoms depend upon degree and duration of obstruction and size of stone
- Symptoms may include recurrent episodes of pain and swelling, usually associated with eating
- Longstanding obstruction may lead to chronic sialadenitis with possible bacterial infection
- Most commonly located in ductal structure of submandibular gland

- Calculi may be physically detectable if of sufficient size and close to ductal orifice
- Treatment
 - Small stones may be removed by manual manipulation
 - Larger stones may require surgical excision

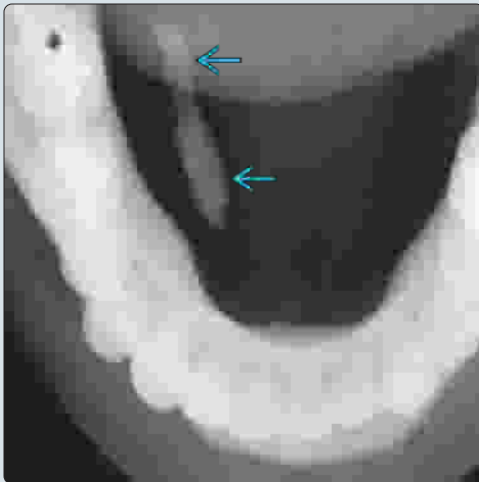
MICROSCOPIC

- Salivary stones are round to ovoid with concentric calcified layers
- Surrounding duct (if present) may display squamous, mucous, or oncocytic metaplasia
- Glandular parenchyma may show fibrosis, acinar atrophy, and mucositis

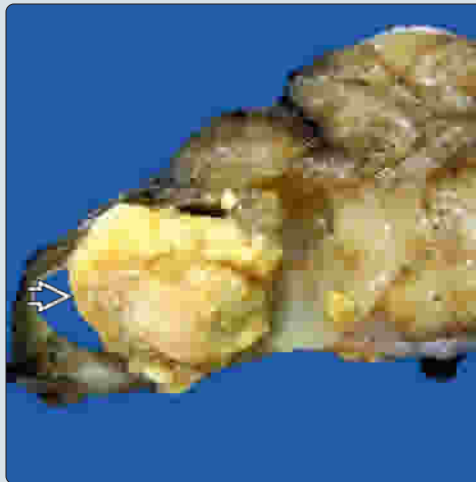
TOP DIFFERENTIAL DIAGNOSES

- Chronic sclerosing sialadenitis
- Intraosseous radiopacity

Radiographic Evidence of a Sialolith

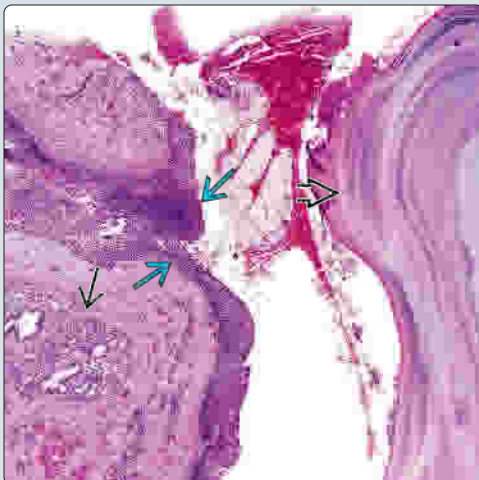


Gross Image of Sialolith

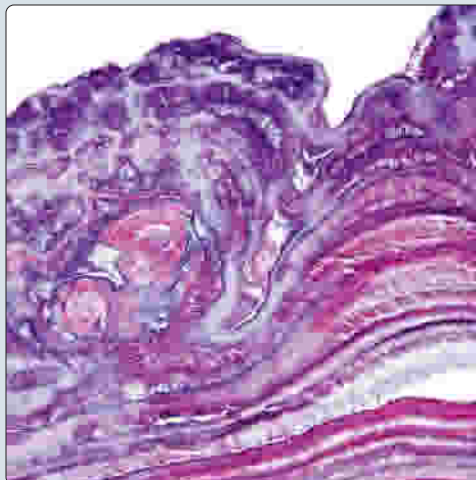


(Left) Occlusal radiograph of the right mandible shows an oblong-shaped sialolith in the Wharton duct of the submandibular gland. This radiograph was intentionally underexposed so the sialolith would not be burned out on the image. Thirty percent of submandibular sialoliths are at the hilum or in the proximal portion of the Wharton duct. (Right) Gross photograph shows a sialolith within a dilated duct from the parotid gland. The calculus is yellow with some crumbling and breakdown seen.

Sialolith in Association With Duct



Concentric Calcified Layers in Sialolith



(Left) This medium-power H&E shows the relationship between the sialolith and the duct it was found in. Note the squamous metaplasia of the duct. A chronic inflammatory infiltrate and the focal chronic sialadenitis are seen in the surrounding tissue. (Right) In this high-power view of a sialolith, note the laminar architectural pattern of the calcifications. The concentric layering suggests a certain length of time for stone formation.

Sclerosing Polycystic Adenosis

KEY FACTS

TERMINOLOGY

- Reactive/neoplastic inflammatory lesion of salivary glands that histologically resembles fibrocystic changes, sclerosing adenosis, and adenosis tumors of breast

CLINICAL ISSUES

- Majority in parotid gland (80%)
- Recurrence possible in ~ 1/3 of cases
- No reports of metastatic spread or related mortality

MICROSCOPIC

- Circumscribed but unencapsulated lobular growth
 - Often surrounded by normal salivary gland tissue
- Acinar-like cells with prominent eosinophilic cytoplasmic granules
- Hyperplastic epithelial proliferation of ductal, tubular, and acinar cells in lobular pattern
- Prominent fibrous sclerosis with focal formation of hyalinized sclerotic nodules

- Epithelial atypia or dysplasia (up to carcinoma in situ) has been noted
- Lobular architecture maintained and no invasive growth

ANCILLARY TESTS

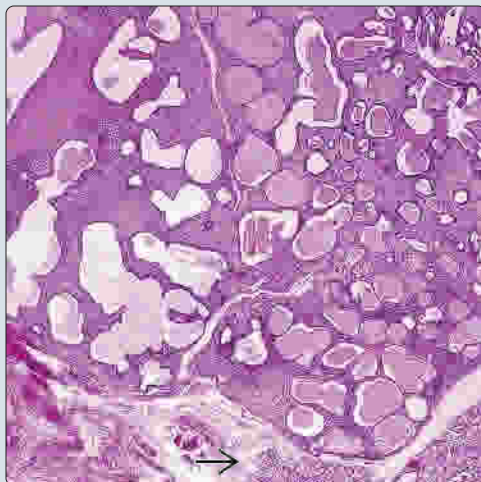
- Myoepithelial cells: **Positive:** S100 protein, smooth muscle actin, and calponin
 - Highlights peripheral myoepithelial cells surrounding ductal and acinar structure even if atypical or dysplastic cells are present

TOP DIFFERENTIAL DIAGNOSES

- Pleomorphic adenoma**
 - Lobular growth pattern of sclerosing polycystic adenosis (SPA) is not normally seen in pleomorphic adenoma
- Chronic sclerosing sialadenitis**
 - Affects submandibular gland and belongs to spectrum of IgG4-related diseases
- Polycystic dysgenetic disease**
 - Fibrosis is not prominent

Sclerosing Polycystic Adenosis

(Left) Low-power view shows a well-circumscribed, lobular epithelial proliferation with variably sized dilated ducts. The surrounding salivary gland parenchyma is unremarkable. (Right) Variable-sized dilated spaces are lined by a thin attenuated ductal epithelium and are surrounded by dense fibrous connective tissue. Intraluminal papillary projections are present and cribriform structures can also occur. Mucin-containing, squamous, sebaceous-like, and ballooned cells can sometimes line the ducts.

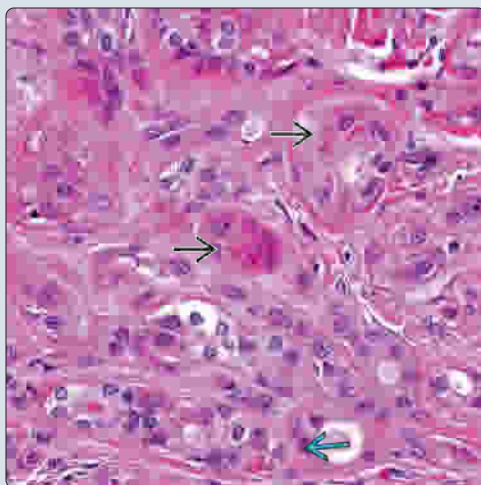


Dilated Ducts With Fibrous Stroma

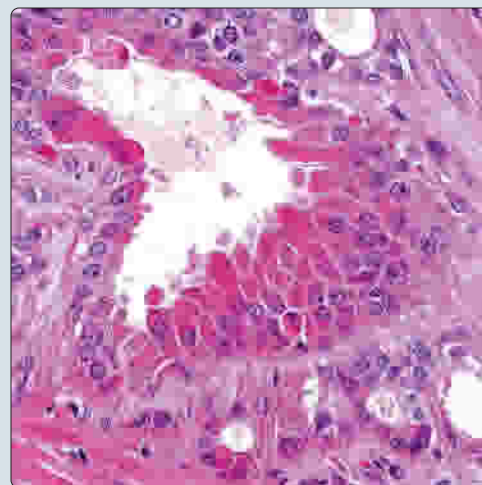


Sclerosing Adenosis-Like Pattern

(Left) High-power view shows numerous small, duct-like structures with irregular elongated ducts. Myoepithelial marker calponin will highlight the periphery of the duct. Focal ductal epithelial cells contain eosinophilic granules ranging in size from fine to very large. Note the fibrosis between the epithelial cells. (Right) High-power view shows an area with apocrine-type secretory change with a ductal structure composed of glandular epithelial cells with bright eosinophilic cytoplasmic granules.



Apocrine-Like Metaplasia



TERMINOLOGY

Abbreviations

- Sclerosing polycystic adenosis (SPA)

Definitions

- Reactive/neoplastic inflammatory lesion of salivary glands that histologically resembles fibrocystic changes, sclerosing adenosis, and adenosis tumors of breast

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare lesion of salivary glands
- Age
 - Children to elderly (9-84 years)
 - Mean presentation: 4th-5th decades
- Sex
 - Females slightly more often than males

Site

- Majority in parotid gland (80%)
 - Occasionally in submandibular or minor salivary glands

Presentation

- Slow-growing, usually asymptomatic mass

Treatment

- Surgical approaches
 - Complete, conservative local surgical excision
 - Conservation of facial nerve in parotid lesions

Prognosis

- Recurrence possible in ~ 1/3 of cases
 - Usually related to incomplete excision or possible multifocal disease
- No reports of metastatic spread or related mortality

MACROSCOPIC

General Features

- Circumscribed, pale, rubbery mass
- May appear multinodular

Size

- Range: 1-12 cm

MICROSCOPIC

Histologic Features

- Circumscribed but unencapsulated
 - Often surrounded by normal salivary gland tissue
- Prominent fibrous sclerosis with focal formation of hyalinized sclerotic nodules
- Hyperplastic epithelial proliferation of ductal, tubular, and acinar cells in lobular pattern
 - May form solid or cribriform nests
 - Cystic dilation may be evident
 - Eosinophilic, spherical, laminated hyaline globules ("collagenous spherulosis") may be noted within epithelial nests
- Glandular epithelial cells vary in appearance

- May include flattened cuboidal, columnar, apocrine-like, mucinous, squamous, and foamy cells
- Acinar-like cells with prominent eosinophilic, PAS (+) cytoplasmic granules
 - Histologically reminiscent of Paneth cells of intestine
- Foamy epithelial cytoplasm likely due to degenerative changes
 - May resemble sebaceous cells
- Nests of xanthomatous macrophages may be present associated with areas of epithelial degeneration
- Epithelial atypia or dysplasia (up to carcinoma in situ) is uncommon
 - Lobular architecture maintained without invasive growth

ANCILLARY TESTS

Immunohistochemistry

- Epithelial cells: **Positive:** Pan-cytokeratin
- Myoepithelial cells: **Positive:** S100 protein, smooth muscle actin, calponin
 - Highlights the peripheral myoepithelial cells surrounding ductal and acinar structure even if atypical or dysplastic cells are present
- Luminal epithelial cells: **Positive:** Estrogen receptors (20%), progesterone receptors (80%)

DIFFERENTIAL DIAGNOSIS

Pleomorphic Adenoma

- Definitive lobular growth pattern of sclerosing polycystic adenosis is not normally seen in pleomorphic adenoma (PA)
- Prominent myoepithelial component and myxochondroid matrix
- Acinar Paneth-like epithelial cells are not seen in PA

Chronic Sclerosing Sialadenitis

- Affects submandibular gland and belongs to spectrum of IgG4-related diseases
- Although fibrosis occurs in both conditions, chronic sclerosing sialadenitis lacks nodular fibrotic pattern of SPA

Polycystic Dysgenetic Disease

- Usually bilateral without recurrences, with limited fibrosis

Salivary Duct Carcinoma

- Characterized by cellular pleomorphism, mitotic figures, comedonecrosis, and invasive growth
- **Positive:** Androgen receptor (strong and diffuse nuclear)

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Pleomorphic Adenoma

KEY FACTS

TERMINOLOGY

- Synonym: Benign mixed tumor
- Benign epithelial tumor that shows epithelial, myoepithelial, and mesenchymal differentiation

CLINICAL ISSUES

- Most common neoplasm of salivary gland origin
- Parotid gland most common site
- Slow growing
- Minor salivary glands 2nd most frequent site affected

MACROSCOPIC

- Recurrent tumors are generally multinodular
- Irregular mass
- Parotid gland
 - Variably thick capsule
 - Rarely unencapsulated
- Minor glands
 - Poorly developed to absent capsule

MICROSCOPIC

- Innumerable cytologic and architectural patterns
 - Solid, tubular, trabecular or cystic
- Duct structures
- Epithelial tissue
 - Spindle, clear, plasmacytoid, basaloid, squamous, sebaceous
- Mesenchymal-like tissue
 - Chondromyxoid, myxoid or hyaline stroma

TOP DIFFERENTIAL DIAGNOSES

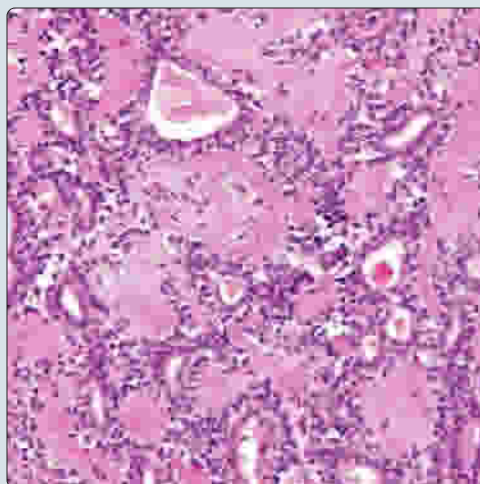
- Myoepithelioma
- Basal cell adenoma
- Adenoid cystic carcinoma
- Polymorphous low-grade adenocarcinoma
- Carcinoma ex-pleomorphic adenoma

DIAGNOSTIC CHECKLIST

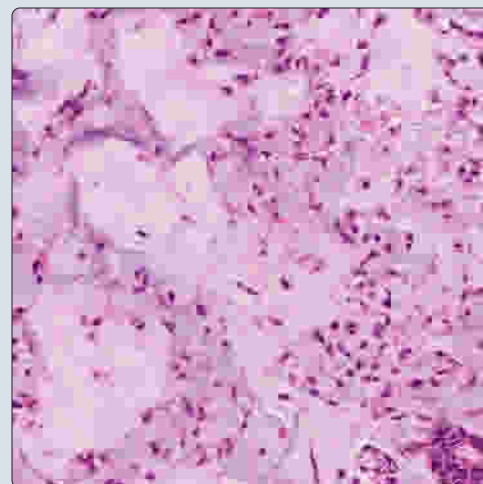
- No 2 look alike

Tubular and Ductal Structures

(Left) This pleomorphic adenoma (PA) shows characteristic areas of tubular and ductal structures with a background of hyaline stroma. PAs show amazing microscopic diversity and many other tumors may be part of the initial differential diagnosis. **(Right)** Hematoxylin & eosin shows a tumor with predominant myxoid stroma with focal epithelial structures. The ratio of epithelium and stroma can vary widely among tumors.



Myxoid Stroma



Varying Patterns of Pleomorphic Adenoma

(Left) Image shows characteristic PA with varying patterns. Ductal structures are closely associated with a myxomatous stroma. **(Right)** Parotid gland tumors have a recurrence rate as high as 8%. When tumors do recur they often times will be multifocal and multinodular. Surgical removal without disruption of the capsule will reduce recurrences. Treatment of multifocal tumors can be difficult and may result in damage to the facial nerve in parotid gland tumors.



Recurrent Pleomorphic Adenoma



TERMINOLOGY

Abbreviations

- Pleomorphic adenoma (PA)

Synonyms

- Benign mixed tumor (BMT)
- Mixed tumor
- Chondroid syringoma
 - Only used if skin/dermis-based tumor

Definitions

- Benign epithelial tumor that shows both epithelial and modified myoepithelial elements mixed with mesenchymal myxoid, mucoid, or chondroid-appearing material
 - Significant architectural diversity rather than cytologic pleomorphism

CLINICAL ISSUES

Epidemiology

- Incidence
 - Most common neoplasm of salivary gland origin
 - 45-76% of all salivary gland neoplasms
 - Comprises ~ 75% of all major salivary gland neoplasms
 - Comprises ~ 40% of all minor salivary gland neoplasms
 - ~ 3/100,000 population
- Age
 - Wide range
 - Peak in 4th-6th decades
 - Most common benign salivary gland tumor in children
- Sex
 - Female > male (slightly) in adults
 - Male > female in children (< 18 years)

Site

- Parotid gland most commonly affected site (~ 80%)
 - Most commonly superficial lobe
 - Inferior (lower pole) or tail of parotid gland
 - Deep lobe less frequently
 - Large lesions may compromise airway
- Minor salivary glands 2nd most common site
 - Palate
 - Most common minor salivary gland site
 - Involves junction of hard and soft palate
 - Unilateral, fixed mass (no soft tissue to allow mobility)
 - Buccal mucosa and upper lip
 - Rarely affects lower lip and tongue
- Uncommon in submandibular and sublingual glands
- Can affect larynx, nasal cavity, ear, orbit, upper aerodigestive tract, gastrointestinal tract
- Rarely, may develop within ectopic salivary gland tissue

Presentation

- Usually, painless, slow-growing mass
- Single, smooth, mobile, firm nodule
 - Rarely, 2nd tumor is found
 - Metachronous vs. synchronous
 - May be identified concurrently with Warthin tumor
- Mucosal ulceration is uncommon
- Paresthesia due to nerve compression is rare finding

- If pain is present, tumor is more likely to be infarcted

Natural History

- Slow growing and asymptomatic
- May reach enormous size if neglected
- Uncommon malignant transformation
 - ~ 7-10% of all PA cases

Treatment

- Options, risks, complications
 - Surgical complications
 - Frey syndrome (gustatory sweating)
 - Decreased muscle control of face (if facial nerve is sacrificed)
 - Capsule disruption may result in seeding of tumor (increases likelihood of recurrence)
 - Enucleation only results in high recurrence rate (up to 50%)
- Surgical approaches
 - Parotid gland
 - Superficial parotidectomy
 - Extracapsular dissection (include rim of uninvolved tissue)
 - Facial nerve preservation when possible
 - Minor glands
 - Conservative, complete surgical excision
 - Submandibular gland
 - Complete excision

Prognosis

- Excellent long-term prognosis, although limited by recurrence and malignant transformation
 - Overall recurrence rate: ≤ 2.5%, most developing within 10 years
- Parotid gland tumors have recurrence rate as high as 8%
 - Recurrences tend to be multinodular or multifocal
- Submandibular and minor salivary gland tumors rarely recur
- Malignant transformation in up to 10% of cases, with the following risk factors
 - Long history of untreated tumor (15 years)
 - Multiple recurrences
 - Age of patient (usually > 40 years)
 - Male gender
 - Tumors > 2 cm in greatest dimension
 - Deep lobe tumors
 - More common in parotid gland

IMAGING

General Features

- Imaging provides information about exact anatomic site, extent of disease, and possible invasion or nodal metastases
- US or CT are complimentary and allow for image-guided fine-needle aspiration (FNA)
 - Excellent resolution and tissue characterization without radiation hazard, especially for superficial lobe lesions
- MR or CT is mandatory to evaluate tumor extent and exclude local invasion
 - Unilateral mass, which shows post-contrast enhancement, has high T2 signal, and does not invade surrounding tissue planes, is most likely PA

Pleomorphic Adenoma

- MR spectroscopy may separate Warthin from PA, although not yet well accepted
- Ultrasonography is especially valuable in children, since most tumors are benign and many are cystic or vascular (color Doppler for latter)
 - High-resolution sonography has nearly 100% sensitivity in detecting intraparotid tumors
 - Precisely outlines tumor borders
 - Can detect multiple or bilateral lesions
- Sialography delineates ductal system but is limited in tumor assessment

MACROSCOPIC

General Features

- Irregular mass
- Fibrous capsule
 - Parotid gland
 - Variably thick incomplete capsule but rarely unencapsulated
 - Minor glands
 - Poorly developed to absent
- Cut surface homogeneous, white to white-tan
- Recurrent tumors are generally multinodular
- Hemorrhage or infarction
 - Secondary to FNA or previous surgical procedures

Size

- Majority between 2-5 cm
- Rarely, may be enormous (up to 25 cm)

MICROSCOPIC

Histologic Features

- Innumerable architectural patterns
 - Solid, tubular, trabecular, or cystic
- Duct structures
 - Lined by cuboidal or columnar epithelium
- Epithelial tissue shows variable morphology
 - Spindle, clear, plasmacytoid, basaloid, squamous, sebaceous
- Mesenchymal-like tissue
 - Chondromyxoid, myxoid or hyaline stroma
 - Calcified (bone) foci may be present
 - Rarely fatty changes
- Rarely, crystals are present
 - Collagenous crystalloids: Eosinophilic needle shapes arranged radially
 - Tyrosine-rich crystalloids: Eosinophilic blunted shapes arranged in tubular architecture
 - Crystalloids resembling oxalate crystals
- Occasionally squamous or sebaceous metaplasia is identified
- Rarely necrosis, but degeneration frequent (especially after FNA)

ANCILLARY TESTS

Cytology

- Findings are variable
- Cellular smears with epithelial and mesenchymal cells and fibrillar background

- Clusters or cohesive groups of epithelial cells
 - Branching trabeculae of cells that drop off into stroma
 - Plasmacytoid or spindle cells
 - Bipolar myoepithelial cells with eccentric round nuclei
 - Spindled cells tend to embed within stroma
 - Round, ovoid to fusiform nuclei
 - Delicate nuclear chromatin distribution
 - Squamous and sebaceous cells may be seen
 - Atypia can be seen but tends to be single cell
- Fibrillar chondromyxoid stroma
 - Feathered edge that blends and surrounds epithelial/myoepithelial cells
 - Cells may line up along edge of matrix, mimicking adenoid cystic carcinoma
 - Pale green with alcohol-fixed Papanicolaou stains
 - Deep purple to magenta with air-dried Romanowsky stains (Diff-Quik, Giemsa)
 - Striking metachromasia with Giemsa
 - Appears different from mucus, necrotic material, or inflammatory debris
- High cellularity with limited stroma should be diagnosed as salivary gland neoplasm to avoid misdiagnosis

Immunohistochemistry

- Immunohistochemistry is sensitive but not specific
- **Panel:** Cytokeratin, p63, GFAP, S100 protein, PLAG1 (nuclear) and SMA are recommended, as all will be variably positive

Genetic Testing

- 4 major cytogenetic abnormalities, with rearrangements involving
 - 8q12 (39%)
 - t(3;8)(p21;q12) and t(5;8)(p13;q12) are most frequently identified translocations
 - Target gene is pleomorphic adenoma gene 1 (*PLAG1*), a zinc finger transcription factor
 - Consistently rearranged and activated, resulting in overexpression in ~ 50% of cases
 - 12q13-15 (8%)
 - t(9;12)(p24;q14-15) or ins(9;12)(p24;q12q15) most frequently identified translocation
 - Target gene is high mobility group protein gene, *HMGA2* (or *HMGIC*), which is overexpressed
 - *HMGA2* encodes architectural transcription factor that promotes activation of gene expression
 - Sporadic clonal rearrangements of other genes (23%)
 - Normal karyotype (30%)
 - More often are stroma rich than tumors with 8q12 abnormalities
- Currently identified 5 *PLAG1*- and *HMGA2*-containing fusion genes are tumor specific
 - *PLAG1* is immunomarker with good specificity for PA
- Infrequent overexpression of p53 oncoprotein (~ 15% of cases), perhaps early event in malignant transformation

DIFFERENTIAL DIAGNOSIS

Myoepithelioma

- Essentially, cellular mixed tumor with no glandular differentiation and no chondromyxoid matrix
- Perhaps part of pleomorphic adenoma spectrum

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CK-PAN	Positive	Cytoplasmic	Both ductal epithelial cells and spindle cells
S100	Positive	Nuclear & cytoplasmic	Myoepithelial cells
GFAP	Positive	Cytoplasmic	Myoepithelial cells and myxoid areas
Actin-sm	Positive	Cytoplasmic	Periductal and spindle cells; negative in plasmacytoid cells
Calponin	Positive	Cytoplasmic	Plasmacytoid cells
p63	Positive	Nuclear	Both ductal epithelial cells and spindle cells
SMHC	Positive	Cytoplasmic	Myoepithelial cells
CD10	Positive	Cytoplasmic	Myoepithelial cells
CK5/6	Positive	Cell membrane & cytoplasm	Nearly all tumor cells
CK7	Positive	Cytoplasmic	Plasmacytoid cells
Vimentin	Positive	Cytoplasmic	Both epithelial and myoepithelial cells
CD117	Negative		May rarely be positive

Basal Cell Adenoma

- Uniform proliferation of basaloid cells
- Absence of chondromyxoid stroma
- Prominent basal lamina encircle nests of cells

Adenoid Cystic Carcinoma

- Cells are predominately uniform in size with oval-to-angulated shape
- Variable patterns but most have areas of amorphous, eosinophilic hyalinized stroma
- Infiltrative with perineural invasion

Polymorphous Low-Grade Adenocarcinoma

- Almost exclusive to minor salivary glands
- Numerous growth patterns, unencapsulated, with perineural invasion
- Uniform oval cells

Carcinoma Ex-Pleomorphic Adenoma

- Infiltrative margins, perineural and vascular invasion
- Marked pleomorphism, mitotic figures, necrosis
- Adenocarcinoma, not otherwise specified, but salivary duct carcinoma common also

Mixed Tumor of Skin (Chondroid Syringoma)

- Essentially same histology but arising from skin

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Clinical Photo of Palate Pleomorphic Adenoma

(Left) A PA affecting the palate shows a smooth, raised nodule within the hard palate. There is no ulceration. This is a nonspecific appearance and may represent several different processes. Biopsy is required in this case. (Right) Sagittal CECT near the midline, reveals a well-circumscribed, mildly enhancing heterogeneous mass in the soft palate. PA and dermoid were both initially considered in the imaging differential diagnosis. (From DI: H&N, 2e.)

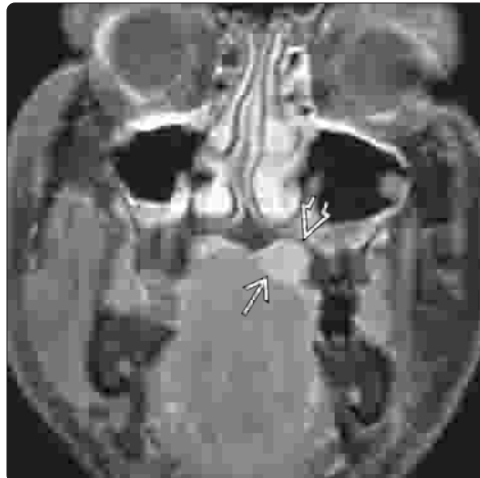


CT of Soft Palate Pleomorphic Adenoma

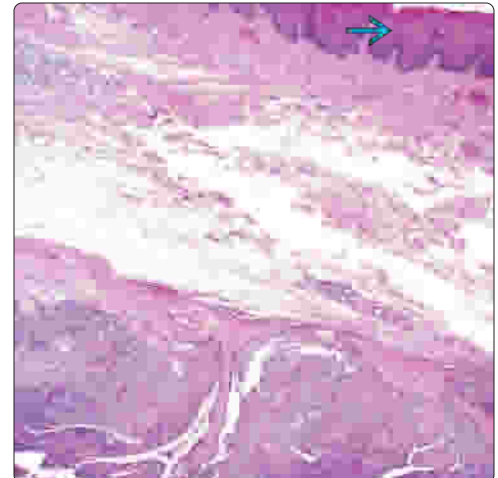


MR of Hard Palate Pleomorphic Adenoma

(Left) Coronal T1WI C+ FS MR shows a moderately enhancing, well-circumscribed left hard palate mass. Hard palate bone is remodeled by a PA. (From DI: H&N, 2e.) (Right) This image is from a PA of the soft palate. The overlying epithelium is intact, although frequently ulcerated in cases like this. The palate is the most common minor salivary gland site for PAs. Clinically, any mass of the palate that is not bony hard to palpation should be considered a salivary gland neoplasm until proven otherwise.

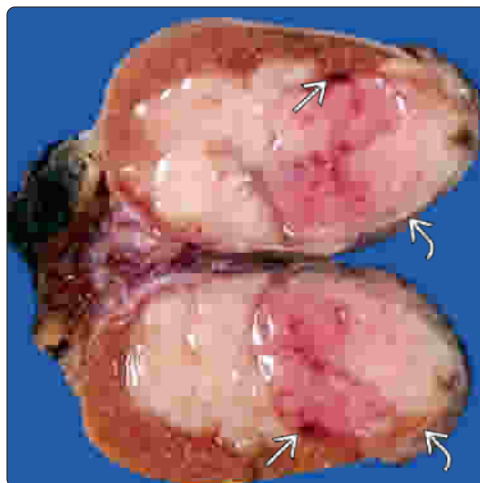


Intact Squamous Epithelium Above Pleomorphic Adenoma

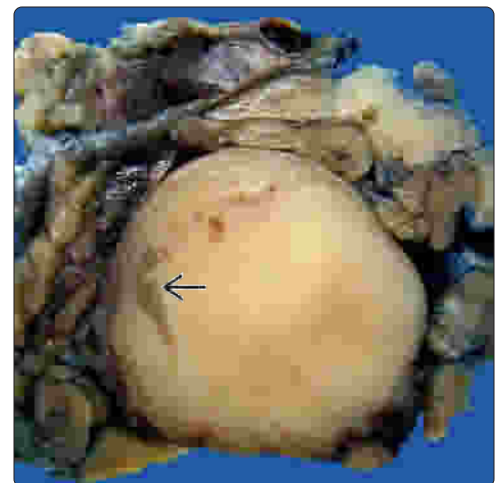


Hemorrhage

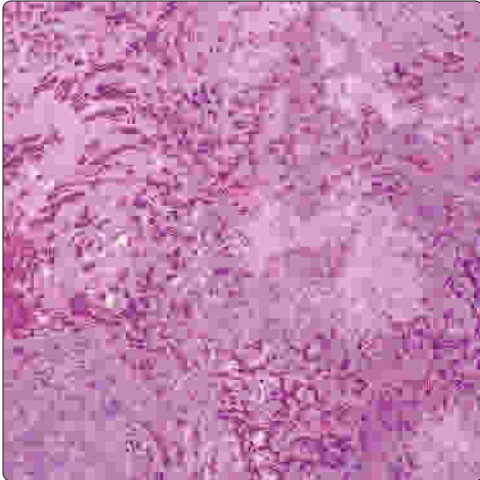
(Left) Gross photograph shows a well-circumscribed, oval pleomorphic adenoma. Bisection shows a tan-pink to white surface and a thin fibrous capsule. Focal hemorrhage may be seen secondary to a fine-needle aspiration (FNA). (Right) Gross photograph shows a formalin-fixed pleomorphic adenoma with well-defined borders surrounded by normal gland and soft tissue. Note the focus of translucent tissue representing an area of chondromyxoid tissue.



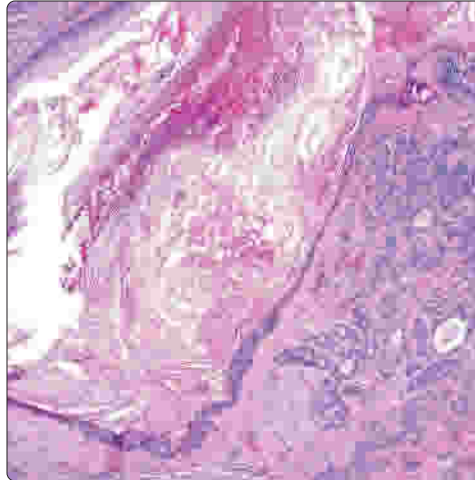
Chondromyxoid Tissue



Anastomosing Strands of Epithelium



Cystic Space in Pleomorphic Adenoma

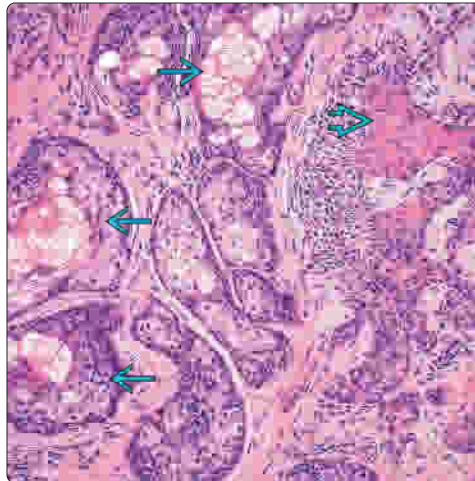


(Left) Hematoxylin & eosin shows myxoid background with islands and anastomosing strands of epithelial cells. This case was accurately diagnosed, prior to excision, based on the aspirate obtained from a fine-needle biopsy. (Right) This image depicts a PA with a central cystic area that contains keratin. Tumors with areas of cystic differentiation should broaden the differential diagnosis. A mucoepidermoid carcinoma should be considered and ruled out.

Fibrous Connective Tissue Capsule

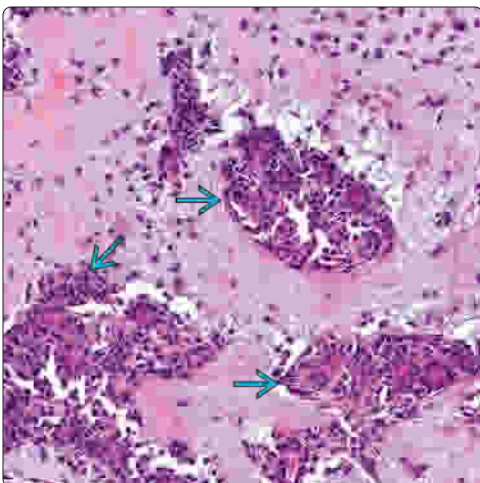


Squamous and Sebaceous Differentiation

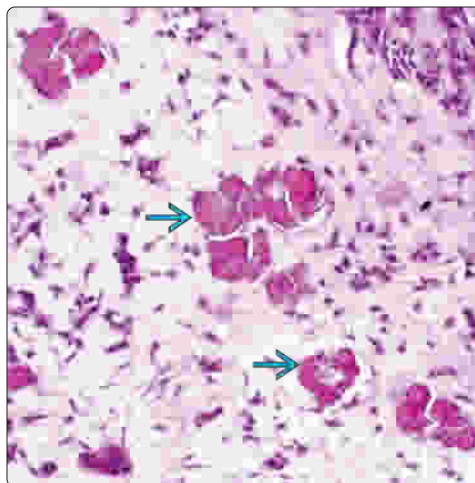


(Left) Hematoxylin & eosin shows a fibrous capsule separating the tumor from the associated salivary gland. Minor salivary gland tumors generally lack a well-formed capsule but are usually well circumscribed. (Right) Pleomorphic adenoma may have areas of squamous or sebaceous differentiation, along with keratinization. Due to the sebaceous differentiation, a sebaceous lymphadenoma may be considered for the differential diagnosis.

Plasmacytoid Cells



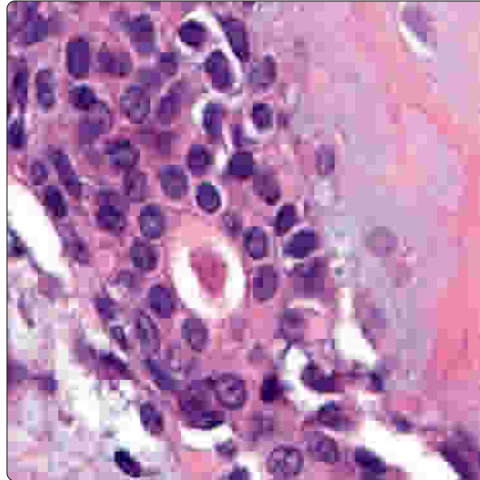
Tyrosine Crystals in Pleomorphic Adenoma



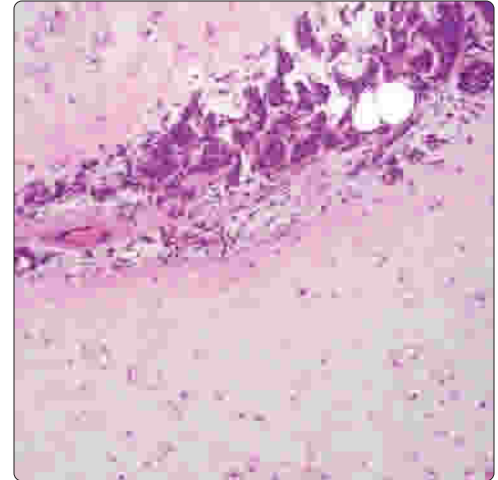
(Left) PA shows focal solid areas composed of oval plasmacytoid cells. A myoepithelioma must be considered in the differential diagnosis when ductal structures are lacking. Ducts were numerous in other areas of this tumor. Also, the chondromyxoid stroma seen is not a feature of monomorphic adenomas. (Right) Hematoxylin & eosin shows tyrosine-rich crystals scattered in a myxoid stroma. Of all salivary gland tumors, PAs are the most common tumors to have crystalloids.

(Left) Hematoxylin & eosin shows a high-power view of a duct lined by round to cuboidal luminal cells adjacent to a focus of myxoid stroma. Ducts are essential to the diagnosis of pleomorphic adenoma; without ducts the diagnosis of myoepithelioma should be considered. **(Right)** Hematoxylin & eosin shows a focus of cartilaginous-like material. Rarely bone and mature fat may be identified.

Duct in Pleomorphic Adenoma

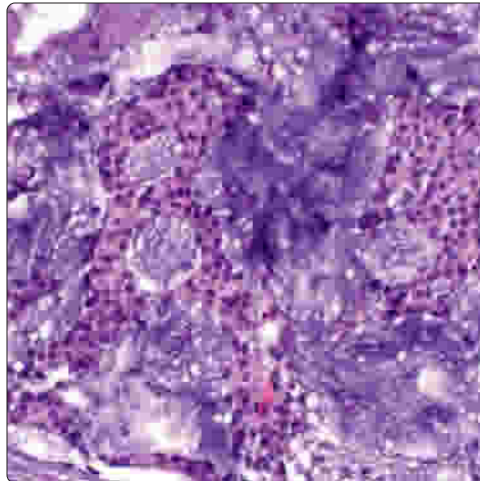


Cartilaginous-Like Focus in Pleomorphic Adenoma

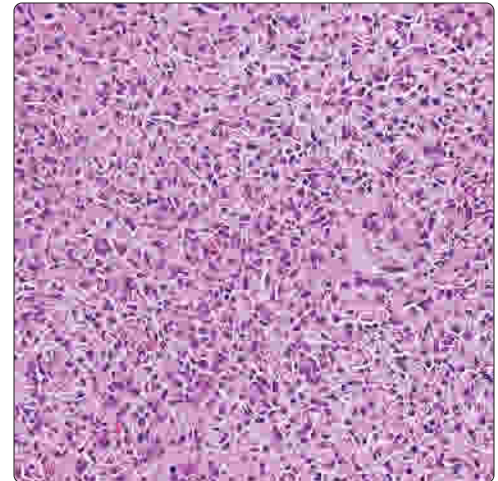



(Left) Hematoxylin & eosin shows the blending of the epithelial cells with the mucinous-myxoid matrix material. Other areas of this tumor have a different appearance, solid and without much matrix material. **(Right)** This image shows a focus of PA without ducts or gland-like structures. A tumor with scant ducts may be referred to as a cellular, or myoepithelial-predominant, PA. Review of multiple levels may be helpful.

Mucinous-Myxoid Matrix Material

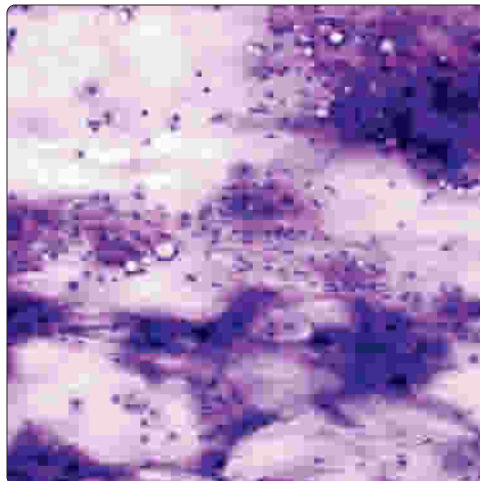


Focus of Myoepithelial-Predominate Pleomorphic Adenoma

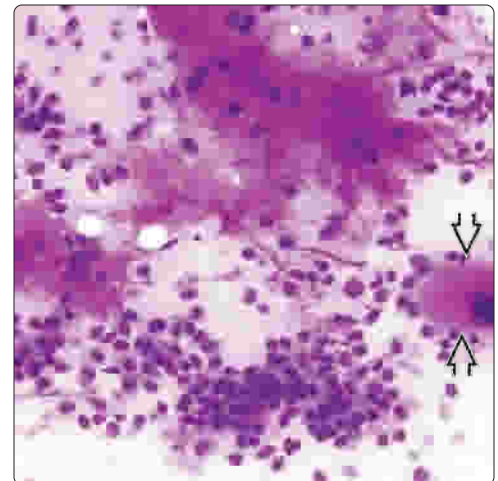


(Left) Diff-Quik shows a fibrillar background stroma and a streaming of epithelial nuclei within the material. There are small collections of epithelial cells intermingled with the background myxoid-matrix material. **(Right)** Diff-Quik shows a bright magenta appearance to the fibrillar chondromyxoid matrix material. Note how the epithelial-myoepithelial cells blend with the matrix, although a single focus  shows a peripheral palisading of nuclei.

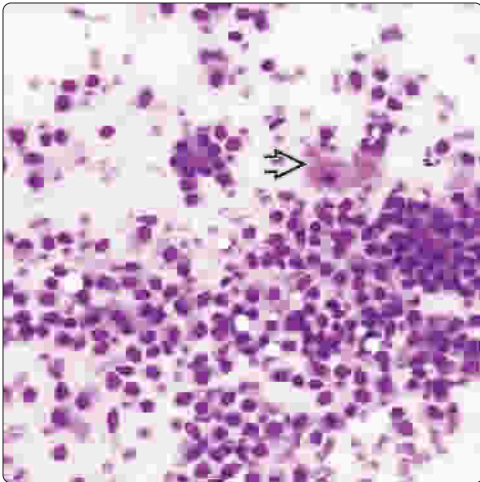
Fibrillar Background in FNA Material



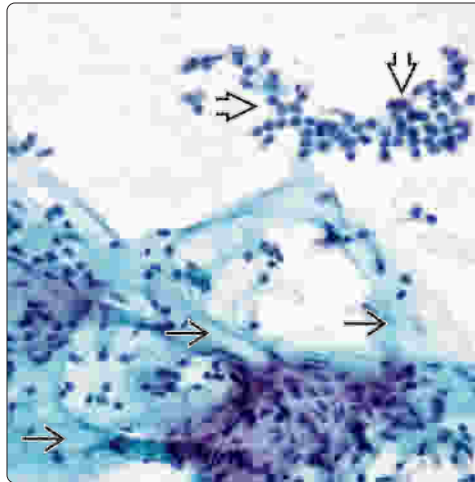
Bright Magenta Fibrillar Matrix in Pleomorphic Adenoma



Cellular Tumor by Diff-Quik Stain

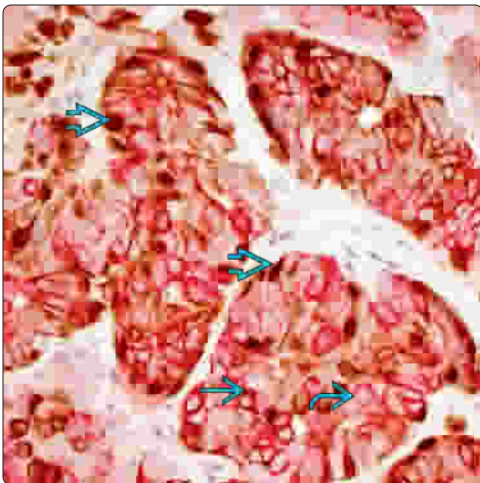


Epithelial Groups in FNA Material

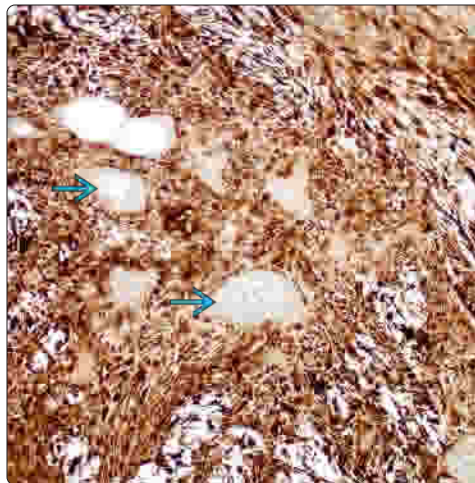


(Left) Diff-Quik shows a much more cellular neoplastic proliferation with only a few foci of matrix material in this cellular PA. The cells have a plasmacytoid appearance, with eccentric nuclei that are round and regular. (Right) Papanicolaou stain shows the epithelial groups as well as the background stroma, although the stroma is much less easy to definitively identify in comparison to the Diff-Quik preparations.

Triple Immunohistochemistry Stain in Pleomorphic Adenoma

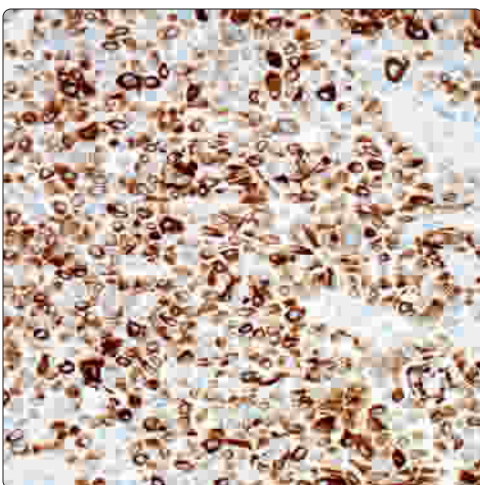


S100 Protein Reacts With Most Tumor Cells

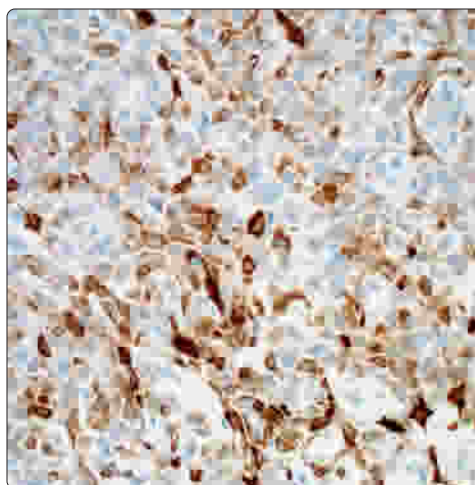


(Left) Triple immunohistochemistry cocktail highlights the membrane of the epithelial cells (EMA), while the cytoplasm of the neoplastic cells is stained light brown (CK5/6), and the nuclei of the basal-myoepithelial cells are highlighted with p63. (Right) S100 protein shows nuclear and cytoplasmic reactivity for myoepithelial cells but has variable reactivity for other cells (squamous cells are negative).

GFAP Yields Strong, Positive Reaction



Calponin Highlights Several Tumor Cells



(Left) Glial fibrillary acidic protein (GFAP) shows dense reactivity for myoepithelial cells in the myxoid areas of the tumor. GFAP is a helpful marker for PA, as it is not usually positive in other salivary gland neoplasms. (Right) There is a strong and diffuse reaction with calponin in the myoepithelial population of this PA.

Myoepithelioma

KEY FACTS

TERMINOLOGY

- Benign salivary gland neoplasm composed entirely of myoepithelial differentiated cells

CLINICAL ISSUES

- ~ 1.5% of all salivary gland and ~ 6% of minor salivary gland neoplasms
- Average: 5th decade (44 years); peak in 3rd to 4th decades
- ~ 1/2 occur in parotid gland; hard or soft palate affected next most frequently
- Benign myoepitheliomas can undergo malignant transformation
 - Especially in longstanding tumors or in tumors with multiple recurrences

MICROSCOPIC

- Typically composed of spindled, epithelioid, or plasmacytoid cells
- Background with variable collagenization

- Chondroid or myxochondroid areas are absent

ANCILLARY TESTS

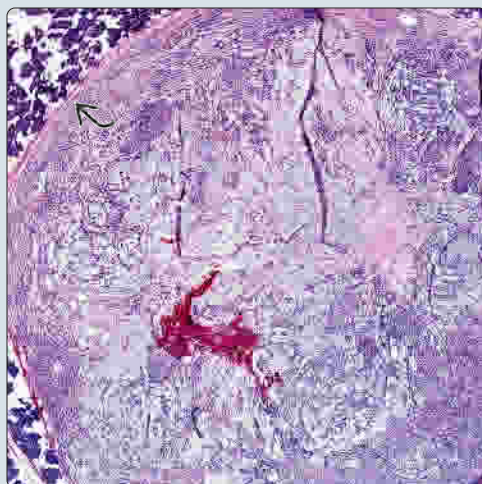
- **Positive:** CK-PAN, CK7, CK14, p63, GFAP, S100 protein, actins, calponin
- *PLAG1* rarely detected, in contrast to pleomorphic adenoma

TOP DIFFERENTIAL DIAGNOSES

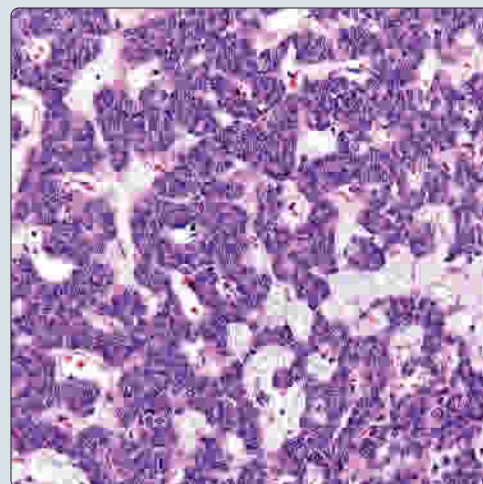
- Pleomorphic adenoma (PA): If ductal structures present, use cellular PA
- Myoepithelial carcinoma: Myoepithelioma lacks necrosis, atypical mitotic figures, or invasion into surrounding parenchyma
- Basal cell adenoma, tubular trabecular type: Composed of 2 cell types; only outer cells are myoepithelial cells
- Plasmacytoma
- Spindled soft tissue neoplasms: Cytokeratin supports epithelial differentiation

Encapsulated Myoepithelioma of Parotid

(Left) A reticular variant of myoepithelioma of the parotid gland, characterized by interconnecting cords with loose vascularized stroma, is shown. The tumor has a well-defined fibrous capsule [□], a feature not generally present in minor salivary gland myoepitheliomas. (Right) Myoepithelioma, composed of spindled to basaloid cells made up of narrow interconnecting cords (reticular pattern) with a myxoid background, is shown. This pattern can be confused with the tubulotrabeular type of basal cell adenoma.

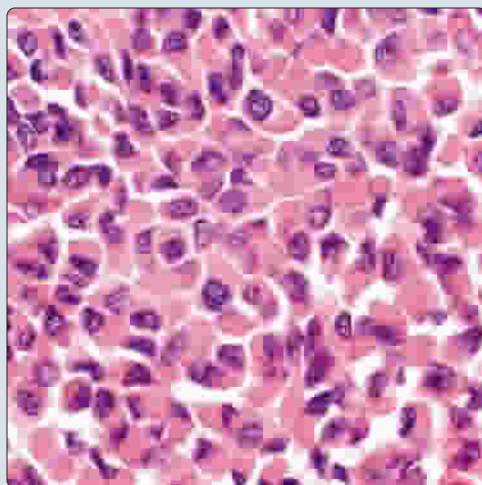


Reticular Pattern of Myoepithelioma

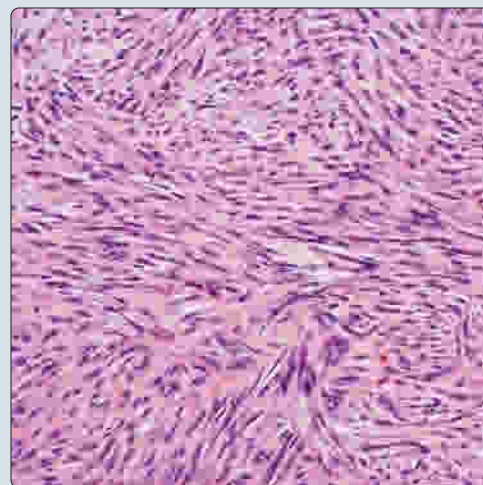


Plasmacytoid Cells in Myoepithelioma

(Left) The nuclei seen here in the plasmacytoid cells are eccentric, surrounded by amorphous eosinophilic cytoplasm. The cytoplasm lacks a "hof" zone of clearing. There is no pleomorphism or necrosis. (Right) Myoepithelioma shows a predominant spindle cell morphology. Tumors of this type are more commonly noted in the major salivary glands. This could be easily confused with leiomyoma or schwannoma. Fascicular or swirling grown patterns can be seen.



Myoepithelioma: Spindle Cell Type



TERMINOLOGY

Synonyms

- Benign myoepithelial tumor

Definitions

- Benign salivary gland neoplasm composed entirely of myoepithelial differentiated cells
 - No discernible ductal component

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~ 1.5% of all salivary gland neoplasms
 - ~ 6% of minor salivary gland neoplasms
- Age
 - Wide range affected
 - Average: 5th decade (44 years)
 - Peak in 3rd to 4th decades
- Sex
 - Equal gender distribution

Site

- ~ 1/2 occur in parotid gland
- Palate (hard or soft) affected next most frequently

Presentation

- Typically asymptomatic
- Slowly growing swelling of affected region
- Painless mass

Treatment

- Surgical excision with tumor-free margins
 - Superficial parotidectomy, wide local excision, or submandibulectomy

Prognosis

- Less likely than pleomorphic adenoma to recur
- Clinical recurrence associated with positive surgical margins
- Benign myoepitheliomas can undergo malignant transformation
 - Especially in longstanding tumors or in tumors with multiple recurrences

MACROSCOPIC

General Features

- Well demarcated, yet variably encapsulated
- Soft gray, white, or yellow-tan mass
- May have rubbery to solid consistency
- Usually < 3 cm; range: 1-5 cm

MICROSCOPIC

Histologic Features

- Well circumscribed but variably encapsulated
- Broad range of appearances due to multiple architectural patterns
 - Solid, myxoid, reticular, nested, cord-like
- Typically composed of spindled, epithelioid, or plasmacytoid cells
 - May have dominant cell type or mixed morphology

- Plasmacytoid cells with hyperchromatic, round to oval nuclei, and abundant, eccentric eosinophilic cytoplasm
 - Characteristic but not pathognomonic
 - Seen in myoepithelioma and pleomorphic adenoma of palate
- Although not common, clear, oncocytic, or mucinous cells may be seen
- Background with variable collagenization
 - May contain abundant acellular mucoid stroma
- Lacks chondroid or myxochondroid matrix
- Lacks infiltration, perineural invasion, profound pleomorphism, necrosis, increased mitotic figures

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** CK-PAN, CK7, CK14, p63, GFAP, S100 protein
- Variable reactivity with actin-sm, actin-HHF-35, SMHC, and calponin
 - Actins reactive in spindled cells but typically nonreactive in plasmacytoid cells
- *TP53* mutations have been observed

In Situ Hybridization

- *PLAG1* rarely detected, in contrast to pleomorphic adenoma

Electron Microscopy

- Shows epithelial (desmosomes) and myoepithelial (myofilaments) differentiation

DIFFERENTIAL DIAGNOSIS

Pleomorphic Adenoma

- If ductal structures are present, diagnose as cellular (myoepithelial-predominant) pleomorphic adenoma

Myoepithelial Carcinoma

- Myoepithelioma lacks necrosis, atypical mitotic figures, or invasion into surrounding parenchyma

Basal Cell Adenoma, Tubular Trabecular Type

- Composed of 2 cell types: Only outer cells are myoepithelial cells

Plasmacytoma

- Perinuclear cytoplasmic clearing ("hof") in plasma cells

Spindled Soft Tissue Neoplasms

- Neural, smooth muscle, or other spindled soft tissue neoplasms may be considered
- Cytokeratin supports epithelial differentiation

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Basal Cell Adenoma

KEY FACTS

TERMINOLOGY

- Benign salivary epithelial neoplasm of small basaloid cells without myxochondroid matrix

CLINICAL ISSUES

- Wide range with peak in 6th-7th decades
- Female > male (2:1)
- Typically asymptomatic, unilateral, solitary mobile swelling
- Membranous variant: Possible skin adnexal neoplasms
- Complete surgical excision

MICROSCOPIC

- 2 possible subtypes of basaloid cells
 - Smaller cells at periphery of tumor nests with scant cytoplasm and round-to-oval deeply basophilic nuclei
 - Larger cells in interior of tumor nests with more abundant cytoplasm and pale staining nuclei
- Solid, trabecular, tubular, and membranous morphologic patterns

- **Solid pattern:** Basaloid nests of variable size
- **Trabecular pattern:** Plexiform nests of basaloid cells
- **Tubular pattern:** Small ductal lumens connected by bands of basaloid cells
- **Membranous pattern:** Variably sized islands of basaloid cells surrounded by eosinophilic hyaline material
 - Nests form jigsaw puzzle-like pattern
 - Membranous pattern may show multinodular growth
- Squamous eddies and small ductal structures possible

ANCILLARY TESTS

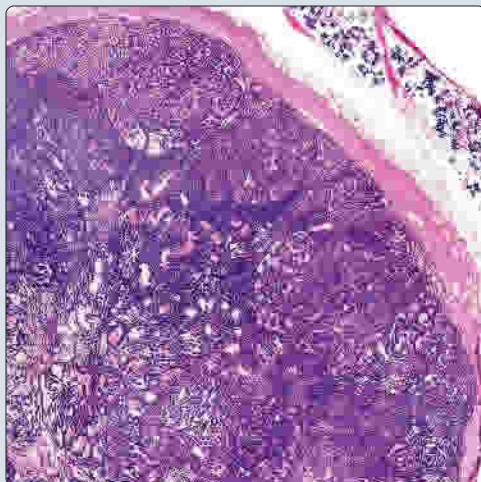
- Keratin strongest in inner, larger basaloid cells; nuclear β -catenin reaction; actin-sm, p63, and calponin strongest in peripheral basaloid cells

TOP DIFFERENTIAL DIAGNOSES

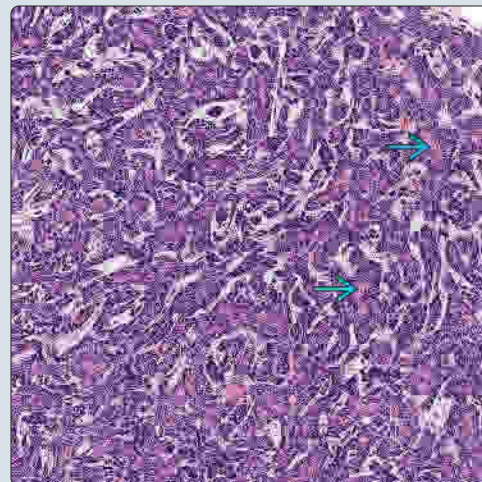
- Basal cell adenocarcinoma, canalicular adenoma, adenoid cystic carcinoma

Encapsulated Basal Cell Adenoma

(Left) This encapsulated basal cell adenoma shows a trabecular and tubular pattern. There is no evidence of invasion. Reduplicated basement membrane material can be seen. (Right) A basaloid neoplastic proliferation shows focal palisading at the periphery. There is a predominantly trabecular architecture. Note the isolated tubules [2].

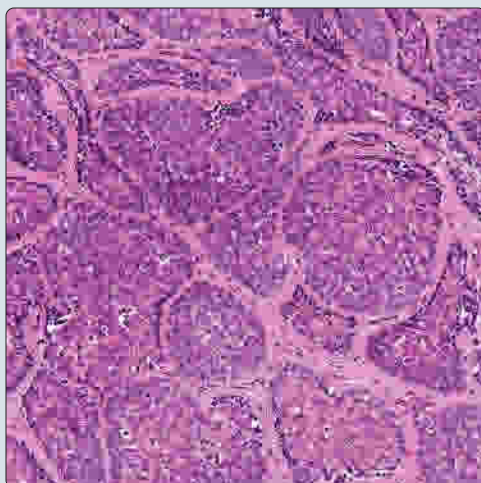


Trabecular Pattern

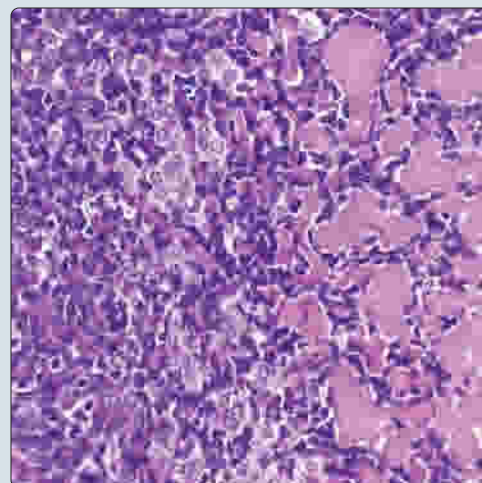


Membranous-Type Basal Cell Adenoma

(Left) This is an example of a basal cell adenoma, membranous type. Variably sized islands of basaloid cells surrounded by eosinophilic hyaline material creating a jigsaw puzzle-like pattern is characteristic of this subtype. (Right) Drop-like eosinophilic hyaline material may be variably present in basal cell adenoma and be surrounded by small basaloid epithelial cells. A solid pattern dominates in this image.



Globular Hyaline Material



TERMINOLOGY

Synonyms

- Membranous subtype: Dermal analogue tumor

Definitions

- Benign salivary epithelial neoplasm composed of basaloid cells lacking chondromyxoid stroma

CLINICAL ISSUES

Epidemiology

- Incidence
 - Represents ~ 2-3% of all salivary gland neoplasia
- Age
 - Wide range with peak in 6th-7th decades
- Sex
 - Female > male (2:1)
 - Membranous type: Slight male predominance

Site

- ~ 75% occur in parotid gland
- Remainder evenly distributed between submandibular gland and lip, palate, and buccal mucosa

Presentation

- Typically asymptomatic, unilateral, solitary mobile swelling of affected gland
- Membranous variant may be multicentric/multifocal
 - Potentially associated with skin adnexal neoplasms
 - Dermal cylindroma (most common), trichoepithelioma, eccrine spiradenoma

Treatment

- Complete surgical excision
 - Conservative excision with rim of normal tissue
 - Membranous variant: Parotidectomy due to possible multifocality

Prognosis

- Recurrence unusual, except for membranous subtype
 - Membranous subtype recurs in up to 25%
 - Evaluate for potential skin adnexal neoplasms
- Malignant transformation highest in membranous type (up to 28%), otherwise ~ 4%

MACROSCOPIC

General Features

- Well-circumscribed, encapsulated nodule
- Membranous type may be multinodular or multifocal
- Cut surface is solid and homogeneous to cystic

Size

- Range: 1-3 cm

MICROSCOPIC

Histologic Features

- All subtypes composed of basaloid cells
 - May display 2 cell morphologies
 - Small cells with scant eosinophilic cytoplasm and round-to-oval deeply basophilic nuclei

- Slightly larger cells with more abundant cytoplasm and pale-staining nuclei
- Smaller cells may palisade at periphery of nests or trabeculae and surround larger, central cells
 - Especially in solid and membranous patterns
- Squamous eddies and small ductal structures possible
- Multiple architectural subtypes
 - **Solid pattern:** Basaloid nests of variable size
 - **Trabecular pattern:** Plexiform nests of basaloid cells
 - **Tubular pattern:** Small ductal lumina connected by bands of basaloid cells
 - Often with trabecular pattern, hence **tubulotrabecular** moniker
 - **Membranous pattern:** Variably sized islands of basaloid cells surrounded by eosinophilic hyaline material
 - Nests form **jigsaw puzzle-like** pattern
 - Peripheral palisading may be conspicuous
 - Nests may contain drop-like hyaline material
 - Most common type to display multifocal growth
- All patterns demonstrate stroma of variable amount and collagenous density
- Major salivary gland tumors may be circumscribed and encapsulated, but multinodular growth simulates invasion

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** Pancytokeratin (strongest in inner, larger cells), S100 protein; actin-sm, p63, and calponin in peripheral, smaller basaloid cells
- **Nuclear β -catenin** reaction (~ 75% of tumors) basaloid myoepithelial cells

Genetic Testing

- *CTNNB1* activating mutation (often c.104T > C, p.I35T)

DIFFERENTIAL DIAGNOSIS

Basal Cell Adenocarcinoma

- Parenchymal invasion, necrosis, numerous mitotic figures
- **Negative:** Nuclear β -catenin reaction (usually)

Canalicular Adenoma

- Upper lip; beaded chains of short columnar cells

Adenoid Cystic Carcinoma

- Parenchymal &/or perineural invasion, cribriform pattern, angular pyknotic nuclei

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Warthin Tumor (Papillary Cystadenoma Lymphomatosum)

KEY FACTS

TERMINOLOGY

- Benign salivary gland tumor characterized by
 - Cystic and papillary growth
 - Presence of bilayered oncocytic epithelial proliferation
 - Presence of associated mature lymphocytic cell stroma

ETIOLOGY/PATHOGENESIS

- Strong link between Warthin tumor (WT) and cigarette smoking

CLINICAL ISSUES

- 2nd most common benign salivary gland tumor (following pleomorphic adenoma)
- Almost exclusively involves parotid gland, particularly in superficial lobe along inferior pole adjacent to angle of mandible
- Complete surgical excision is treatment of choice
- Locally recurrent tumor may occur related to inadequate excision or to multicentrically occurring neoplasms

- Bilateral tumors seen in up to 10% of cases and multifocal tumors in up to 12% of cases

MICROSCOPIC

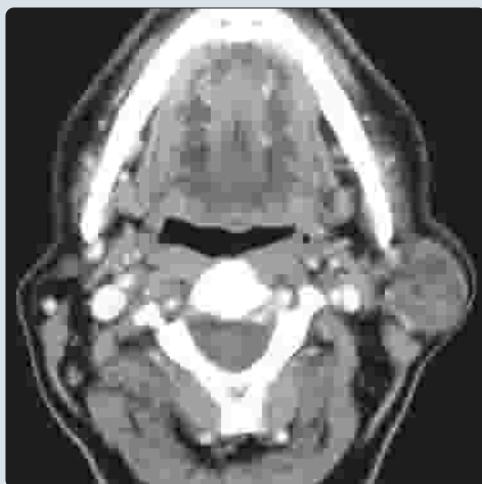
- Epithelial component lining papillary projections composed of double layer of granular eosinophilic cells (referred to as oncocytic epithelia)
- Lymphoid component predominantly composed of mature lymphocytes containing lymphoid follicles with germinal centers
- Metaplastic or infarcted variant of WT
 - Accounts for < 10% of all WT
 - Most likely develops following prior manipulation (e.g., fine-needle aspiration biopsy)
 - Extensive necrosis with ghost-like papillary structures
 - Squamous metaplasia
 - Mucous cell metaplasia

ANCILLARY TESTS

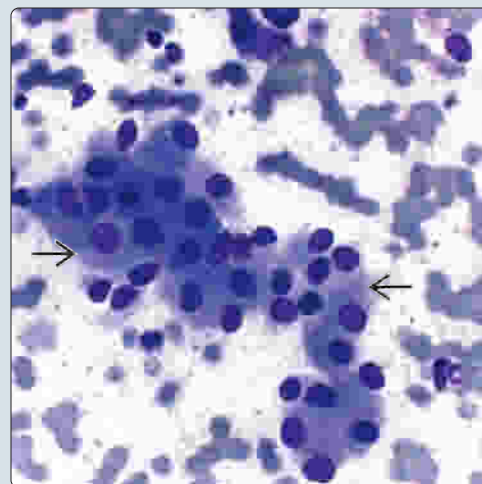
- Absence of *CRTC1/MAML2* fusion transcript

Warthin Tumor: CT Imaging

(Left) CT imaging shows a Warthin tumor (WT) within the tail of the superficial lobe of the left parotid over the angle of the mandible with classic marked heterogeneity and heterogeneous contrast enhancement. (Right) Primary diagnostic evaluation of salivary gland lesions includes fine-needle aspiration. The presence of clusters of oncocytic-appearing epithelial cells with scattered mature lymphocytes in the background supports a diagnosis of WT (Diff-Quik).

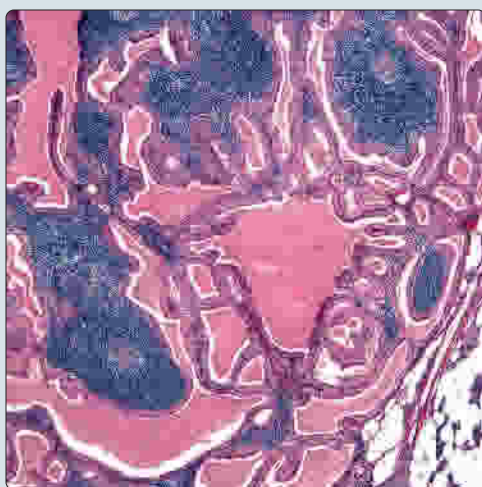


Warthin Tumor: Cytopathologic Findings



Warthin Tumor: Classic Histology

(Left) Classic histology of WT includes cyst formation, papillary architecture, oncocytic epithelium, and an inflammatory cell infiltrate in the walls of the cysts. (Right) Granular eosinophilic (oncocytic) cells are composed of luminal columnar cells with hyperchromatic nuclei aligned toward the luminal aspect and basal cuboidal cells with vesicular nuclei.



Warthin Tumor: Cyst Epithelial Lining



TERMINOLOGY

Abbreviations

- Warthin tumor (WT)

Synonyms

- Adenolymphoma, cystadenolymphoma, papillary cystadenoma lymphomatosum

Definitions

- Benign salivary gland tumor characterized by
 - Cystic and papillary growth
 - Presence of bilayered oncocytic epithelial proliferation
 - Presence of associated mature lymphocytic cell stroma

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Strong link between WT and cigarette smoking
- Radiation exposure linked as tumorigenic factor

Infectious Agents

- Role of Epstein-Barr virus (EBV), human papillomavirus (HPV), and human herpesvirus-8 (HHV-8) in development of WT suggested but not substantiated

Pathogenesis

- Felt to develop from neoplastic transformation of entrapped salivary duct epithelium within intra- and periparotid lymph nodes

CLINICAL ISSUES

Epidemiology

- Incidence
 - 2nd most common benign salivary gland tumor (following pleomorphic adenoma)
 - Accounts for ~ 5-6% of all salivary gland tumors
 - Represents up to 12% of benign parotid gland tumors
- Age
 - Occurs over wide range, but most common in 5th-7th decades of life
 - Uncommon in first 3 decades of life
- Sex
 - Male > female, but
 - Evidence shows marked decline in incidence in men with increased prevalence in women
 - Demographic changes linked to smoking habits (declining use by men, increasing use by women)

Site

- Almost exclusively involves parotid gland, particularly in superficial lobe along inferior pole adjacent to angle of mandible
 - Rare cases reported in submandibular gland, palate, lip, tonsil, larynx, and maxillary sinus
- Bilateral tumors seen in up to 10% of cases and multifocal tumors in up to 12% of cases
 - Bilateral or multifocal tumors may occur synchronously or metachronously

Presentation

- Most common symptom is painless mass

Natural History

- May occur synchronously or metachronously with other salivary gland tumors including
 - Pleomorphic adenoma (most common), monomorphic adenomas, oncocytoma, basal cell adenoma
 - Acinic cell adenocarcinoma, ductal adenocarcinoma, and adenoid cystic carcinoma

Treatment

- Surgical approaches
 - Complete surgical excision is treatment of choice
 - Should include adequate margin of uninvolved tissue
 - Facial nerve should be preserved

Prognosis

- Locally recurrent tumor may occur related to inadequate excision or to multicentrically occurring neoplasms
- Transformation to malignant WT exceedingly rare (incidence of < 0.1%) and may include
 - Epithelial component (carcinoma ex WT)
 - Squamous cell carcinoma (most common), oncocytic carcinoma, adenocarcinoma not otherwise specified, undifferentiated carcinoma, mucoepidermoid carcinoma
 - May metastasize to regional lymph nodes
 - Distant metastasis rare
 - Lymphoid component
 - Malignant lymphoma, usually non-Hodgkin type

IMAGING

Radiographic Findings

- Radionuclide imaging
 - Increased uptake of Tc-99m, which does not wash out following sialogue administration

MACROSCOPIC

General Features

- Encapsulated, soft and fluctuant, round-to-oval mass with smooth or lobulated surface
- On cut section, appears tan-brown with multiple cystic spaces within which papillary projections may be seen
 - Mucoïd or brown exudate may be expressed from cysts

Size

- 1-8 cm in diameter

MICROSCOPIC

Histologic Features

- Papillary and cystic lesion composed of epithelial and lymphoid components
- Epithelial component lining papillary projections composed of double layer of granular eosinophilic cells (referred to as oncocytic epithelia)
 - Inner or luminal cells: Nonciliated, tall columnar cells with nuclei aligned toward luminal aspect
 - Prominent oncocytic appearance of cells is due to presence of increased mitochondrial content
 - Outer or basal cells: Round, cuboidal, or polygonal cells with vesicular nuclei

Warthin Tumor (Papillary Cystadenoma Lymphomatosum)

- Lymphoid component predominantly composed of mature lymphocytes containing lymphoid follicles with germinal centers
 - Epithelial component is sharply demarcated from lymphoid component
 - Other inflammatory cells may be seen, including plasma cells, histiocytes, mast cells, and occasional multinucleated (Langhans-type) giant cells
- Lumina of cysts may contain thick secretions, cholesterol crystals, cellular debris, or corpora amylacea-like laminated bodies
- Squamous metaplasia and focal necrosis may be seen in association with secondary inflammation
- Due to presence of oncocytic cells, WT is subject to degenerative alterations
 - Occurs spontaneously or following manipulation (e.g., post fine-needle aspiration biopsy) including
 - Infarction and necrosis
 - Cytologic atypia
 - Metaplasia, including squamous and mucous cell
 - Granulation tissue, inflammation, fibrosis, hemorrhage
 - Pseudoinfiltrative growth pattern
- Metaplastic or infarcted variant of WT
 - Accounts for < 10% of all WT
 - Most likely develops following prior manipulation (e.g., fine-needle aspiration biopsy)
 - Extensive necrosis with ghost-like papillary structures
 - Residual noninfarcted foci of tumor may be present
 - Squamous metaplasia
 - Often includes keratinization and intercellular bridges
 - Mucous cell metaplasia
 - Cytologic atypia may be prominent, as well as increased mitotic figures, but devoid of atypical mitoses
 - Extensive fibrosis with dense collagen and reactive myofibroblasts may be seen along periphery

ANCILLARY TESTS

Cytology

- Aspiration may yield thick, tannish-brownish fluid; fluid may suggest presence of mucus
- Combination of oncocytic-appearing epithelial cells and mature lymphocytes
- Oncocytic epithelial cells appear in cohesive clusters as well as individual cells and may take on honeycomb arrangement characterized by
 - Abundant granular and eosinophilic cytoplasm
 - Uniform round nuclei with identifiable nucleoli
 - Distinct cell borders
 - Absence of lymphocytes in epithelial clusters
- Background of aspirate may appear "dirty" with cellular debris and associated lymphoid cells

Immunohistochemistry

- All epithelial cells are (pan)cytokeratin **positive**
 - Luminal (or inner) epithelial cells are CK7, CK8 and CK18, and EMA **positive**
- S100 protein, p63, calponin, GFAP, and actin **negative**
- Lymphoid cells reactive for B-cell (CD20) and T-cell (CD3) markers, as well as CD56, CD4 (helper cells), and CD8 (suppressor cells)

Genetic Testing

- Absence of *CRTC1/MAML2* fusion transcript
 - Fusion commonly found in mucoepidermoid carcinomas
 - Similar translocation and fusion transcript reported in WT but not substantiated

DIFFERENTIAL DIAGNOSIS

Cystadenoma

- Lack characteristic features associated with WT including
 - Bilayered epithelial layer and prominent dense lymphoid stroma with germinal centers

Salivary Gland Tumors With Oncocytic Cells

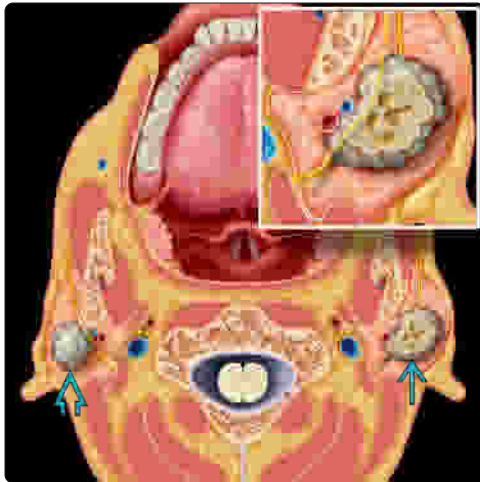
- Oncocytes may be seen in wide variety of tumors/lesions (e.g., oncocytoma, mucoepidermoid carcinoma, acinic cell carcinoma, others)
 - Absence of characteristic bilayered epithelial layer and prominent dense lymphoid stroma of WT

SELECTED REFERENCES

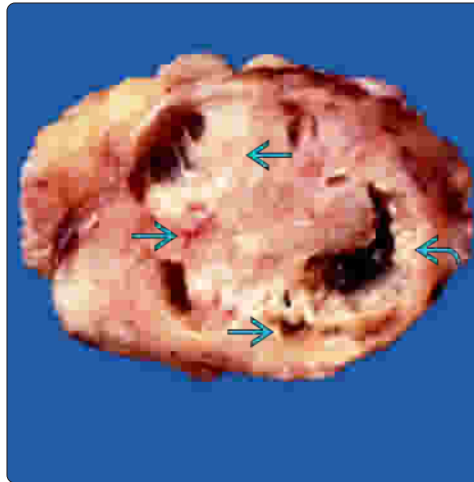
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Warthin Tumor (Papillary Cystadenoma Lymphomatosum)

Schematic Image of Bilateral Warthin Tumor

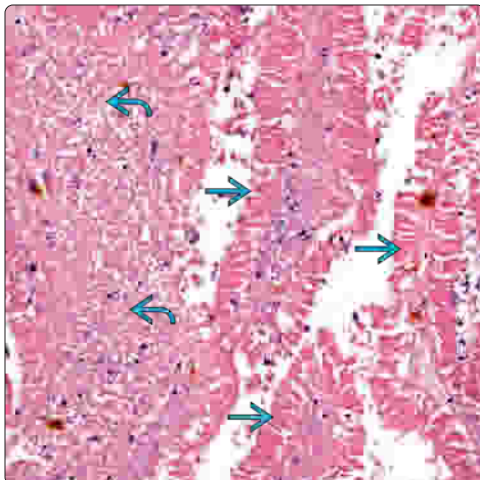


Infarcted Warthin Tumor

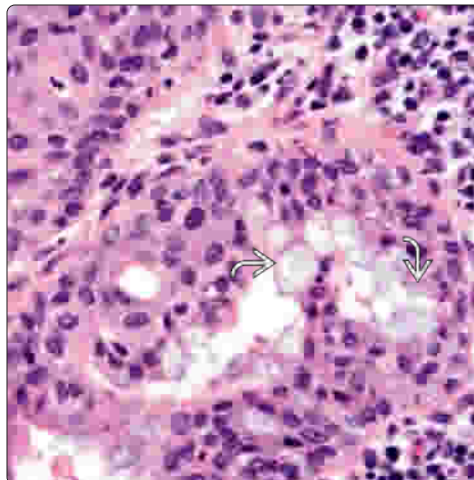


(Left) WT is located in the superficial lobe of right parotid gland [1]. Inset: The facial nerve courses around the tumor but is free of involvement. In 10% of patients, WT may be bilateral, involving the opposite (left) parotid gland [2]. (Right) Resected WT of the parotid gland shows cystic, solid, and focal papillary [3] growth. The central area has the flesh-colored appearance of lymphoid tissue. There are foci of necrosis [4] that occurred secondary to a prior fine-needle aspiration.

Infarcted Warthin Tumor: Residual Structures

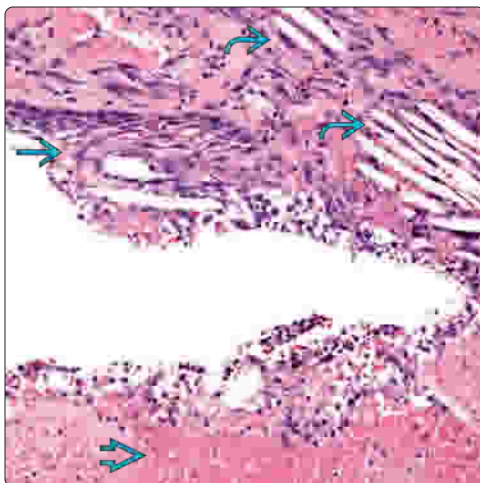


Warthin Tumor With Metaplastic Changes

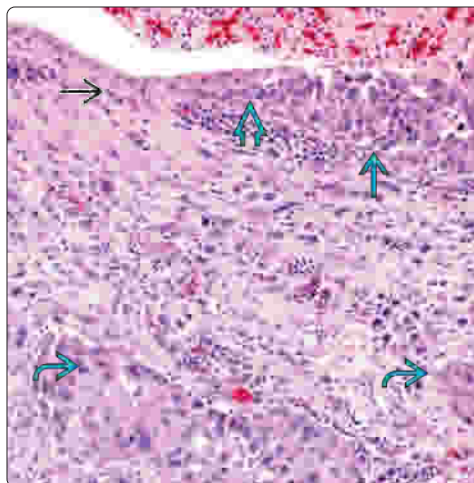


(Left) Metaplastic or infarcted variant of WT shows extensive necrosis with residual ghost-like papillary structures, including oncocytic epithelium [1] and lymphoid cell component [2]. (Right) Mucous cell metaplasia [3] in WT is shown. The presence of mucous cells and squamous/epidermoid cells may suggest a diagnosis of mucoepidermoid carcinoma (MEC). Residual viable &/or infarcted WT and absence of CRTC1-MAML2 translocation assist in differentiating WT from MEC.

Warthin Tumor With Retrogressive Changes



Malignant Transformation of Warthin Tumor



(Left) Infarcted WT shows squamous metaplasia [1] and cholesterol granulomas [2]. Necrosis is present [3]. In such examples, cytologic atypia may be prominent and mitotic figures may be seen, but atypical mitoses and invasive growth are not present, excluding a possible diagnosis of carcinoma. (Right) Malignant transformation of WT shows transition [4] from benign epithelium of WT [5] to carcinoma [6] and invasive undifferentiated carcinoma [7].

KEY FACTS

TERMINOLOGY

- Benign salivary gland neoplasm composed exclusively of large polygonal epithelial cells containing abundant, abnormal mitochondria (oncocytes)

CLINICAL ISSUES

- Mean: 6th-8th decades
- Parotid >> submandibular gland
- Asymptomatic, slow-growing swelling or mass
 - ~ 7% of patients have bilateral tumors

MACROSCOPIC

- Usually solitary, soft, well circumscribed

MICROSCOPIC

- Single nodule, distinct from surrounding parenchyma
- Variable architecture: Solid, acinar, trabecular
- Composed entirely of oncocytes or oxyphilic cells
 - Large, polygonal cells (2x size of acinar cells)

- Abundant, eosinophilic, finely granular cytoplasm
- Distinctive and prominent cell borders
- Intracytoplasmic glycogen may accumulate, giving clear appearance
- Lymphocytes are focally minimal to absent

ANCILLARY TESTS

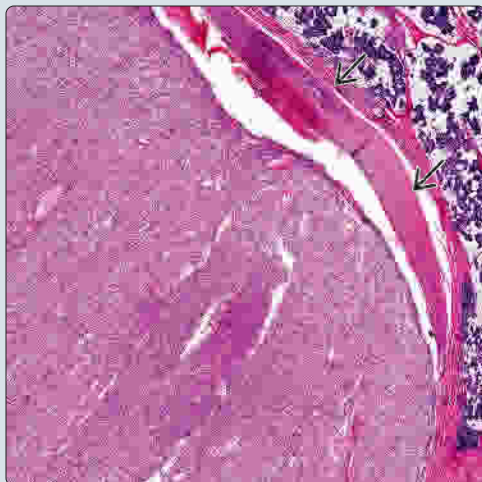
- Immunohistochemistry
 - **Positive:** EMA, CK5/6, CK8/18, CK7, α -1-antitrypsin, antimitochondrial antibody; p63 (basal cells only)
 - **Negative:** Pax-8, S100 protein, actins (SMA, MSA)
- Mitochondrial stains are positive: PTAH, Novelli
- EM shows cytoplasm filled with mitochondria

TOP DIFFERENTIAL DIAGNOSES

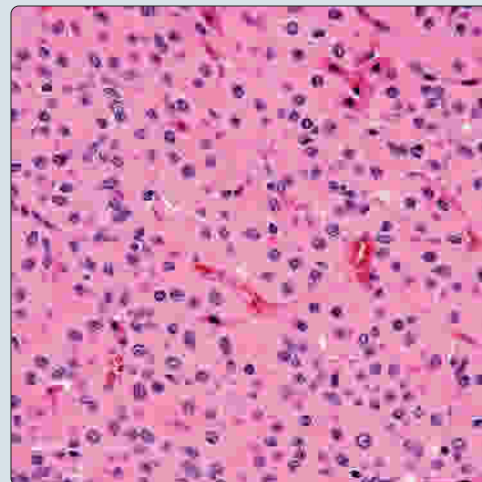
- Nodular oncocytic hyperplasia, oncocytic metaplasia
- Papillary cystadenoma lymphomatosum, mucoepidermoid carcinoma, clear cell tumors

Encapsulated Oncocytoma

(Left) There is an encapsulated tumor, separated from the surrounding parotid parenchyma by a thick and well-formed fibrous connective tissue capsule [2]. The tumor is composed of only oncocytes. **(Right)** The neoplastic cells are large polygonal cells with brightly eosinophilic granular cytoplasm. The nuclei are round and regular with coarse to vesicular nuclear chromatin distribution. A delicate fibrovascular stroma separates the cells.

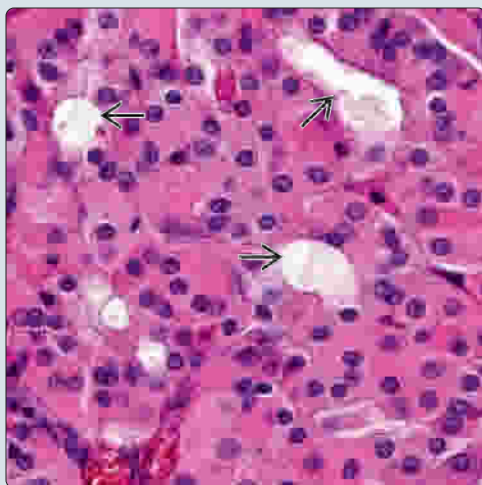


Oncocytes

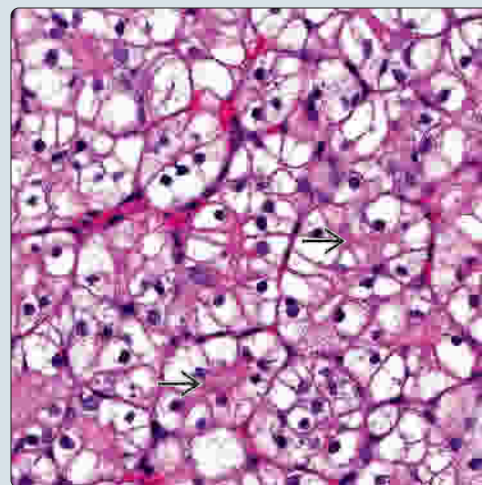


Glandular Oncocytoma

(Left) At high power, the oncocytoma shows a glandular architecture, with the lumen easily identified [2]. The cells are polygonal, containing abundant eosinophilic, granular cytoplasm. The nuclei are round. **(Right)** The clear cell oncocytoma has cleared cytoplasm, creating very prominent and well-formed cell borders. Note a few areas still show oncocytic features [2]. This is a mimic of metastatic renal cell carcinoma.



Clear Cell Oncocytoma



TERMINOLOGY**Synonyms**

- Oncocytic adenoma
- Oxyphilic adenoma

Definitions

- Benign salivary gland neoplasm composed exclusively of large polygonal epithelial cells containing abundant, abnormal mitochondria (oncocytes)
 - By definition, no features of other types of salivary gland neoplasms

ETIOLOGY/PATHOGENESIS**Environmental Exposure**

- Ionizing radiation (~ 20% of patients)
 - Therapeutic or occupational, usually 5 or more years earlier
 - Patients with radiation exposure present on average 20 years younger than patients without radiation exposure

Pathogenesis

- Striated ducts: Normally contain many mitochondria
- Aging
 - Oncocytic metaplasia increases with advancing age (especially in parotid)
 - May be internal derangement or reaction to extracellular environment

CLINICAL ISSUES**Epidemiology**

- Incidence
 - ~ 1.5% of all salivary gland neoplasms
 - Up to 3% of parotid gland neoplasms
- Age
 - Mean: 6th-8th decades
 - About 20 years younger for radiation-exposed patients
 - Younger (mean: 58 years) for submandibular tumors
 - Not a tumor that develops in children
- Sex
 - Slight female predominance
 - Significant female bias for clear cell type oncocytoma

Site

- Parotid > > submandibular gland
- Minor salivary glands: Lower lip, palate, pharynx, buccal mucosa

Presentation

- Asymptomatic, slow-growing swelling or mass
- ~ 7% of patients have bilateral tumors
- Pain or discomfort rarely reported
- Symptoms usually present for long duration (2 years)

Treatment

- Surgical approaches
 - Complete surgical excision is curative (parotidectomy)
 - May have multifocal or bilateral disease
- Radiation
 - Not employed, as oncocytes are radioresistant

Prognosis

- Minimal recurrence with adequate excision
 - Local recurrence may represent multiple &/or bilateral disease
 - Recurrence may develop after long delay (13 years)
- If tumors are bilateral, there is increased risk of recurrence
- Questionable malignant transformation

IMAGING**Radiographic Findings**

- Tc-99m increased uptake and prolonged retention, retained after sialogogue administration
 - Related to increased mitochondrial content

CT Findings

- Usually shows well-defined area of increased density

MACROSCOPIC**General Features**

- Usually solitary
 - Different from nodular oncocytic hyperplasia: Multiple small nodules
- Soft, well circumscribed to partially encapsulated
- Tan to light brown nodule, rarely cystic

Size

- Range: 0.5-7 cm (mean: 3.5 cm)

MICROSCOPIC**Histologic Features**

- Well circumscribed with variably thick capsule
- Should be single nodule, distinct from surrounding parenchyma
 - Rare oncocytes can be seen in surrounding parenchyma, but not in nodules
- No evidence of invasion
- Variable architecture
 - Solid, acinar or ducts (small lumen), trabecular (serpentine cords), papillary, cystic, follicular
- Composed entirely of oncocytes or oxyphilic cells
 - Large polygonal cells (2x size of acinar cells) without pleomorphism
 - Abundant, eosinophilic, finely granular cytoplasm
 - Due to high numbers of mitochondria
 - Uniform, central nuclei with coarse chromatin
 - Prominent nucleoli may be seen
 - 2 cell types can be seen, depending on eosinophilia
 - **Light cells:** Abundant oncocytic cytoplasm surrounding oval vesicular nucleus
 - **Dark cells:** Brightly eosinophilic cytoplasm with pyknotic nucleus
 - Distinctive and prominent cell borders
- Intracytoplasmic glycogen may accumulate, giving clear appearance
- Delicate, fibrovascular stroma
 - Stromal hyalinization, vascularity, or degeneration is possible
- Lymphocytes are focally minimal to absent
- Mitoses are uncommon

Clear Cell Variant If Clear Cells Predominate

- Clearing is fixation artifact &/or intracytoplasmic glycogen deposition

ANCILLARY TESTS**Cytology**

- Usually cellular aspirates
- Show polygonal epithelial cells in papillary fragments, sheets, acinar-like structures, or singly
- Large cells with abundant granular cytoplasm
- Prominent nucleoli may be noted
- There are **no** background lymphocytes

Histochemistry

- Mitochondrial stains are positive
 - Phosphotungstic acid-hematoxylin (48 hour incubation; deep blue granules)
 - Novelli, Cresyl echt violet V, Klüber-Barrera Luxol fast blue
- PAS ± diastase highlights glycogen in clear cells

Immunohistochemistry

- **Positive:** EMA, CK5/6, CK8/18, CK7, CK19, α-1-antitrypsin, SDHB, antimitochondrial antibody; p63 (basal cells only)
- **Negative:** Pax-8, S100 protein, calponin, GFAP, actins (SMA, MSA)

Genetic Testing

- Rarely, mitochondrial DNA mutations may be detected

Electron Microscopy

- Cytoplasm is filled with mitochondria (~ 60% of volume)
 - Irregularly shaped mitochondria frequently show abnormal, elongated cristae with partial lamellar substructure
- Irregular nuclei with inclusions and glycogen granules

DIFFERENTIAL DIAGNOSIS**Nodular Oncocytic Hyperplasia**

- Separation of hyperplasia from neoplasia is arbitrary in many cases
 - Distinction is clinically irrelevant
- Generally not clinical mass
 - Generalized gland involvement (bilateral) can be seen
- Lacks well-developed capsule
- Multiple, topographically distinctive, variably sized nodules
- Rarely, diffuse process affecting entire gland (oncocytosis)
- Involves all cell types, including striated ducts, acinar cells
 - Intermingling of oncocytes with normal acinar elements

Oncocytic Metaplasia

- Normal salivary gland elements and tumors can have areas of oncocytic metaplasia
- Pleomorphic adenoma, basal cell adenoma, cystadenoma, mucoepidermoid carcinoma, and polymorphous low-grade adenocarcinoma are tumors that most frequently exhibit oncocytic metaplasia (without change in diagnostic category)

Papillary Cystadenoma Lymphomatosum (Warthin Tumor)

- Characteristic papillary-cystic architecture with bilayered epithelium
- Oncocytes make up epithelial component of tumor
- Lymphoid stroma (even on FNA material) is hardly ever seen in oncocytoma

Mucoepidermoid Carcinoma (MEC)

- Mucocytes are very rare in oncocytoma, but required for MEC along with epidermoid and intermediate cells
- Invasion, frequently cystic, increased mitoses and pleomorphism
- Organoid architecture **not** usually present in MEC

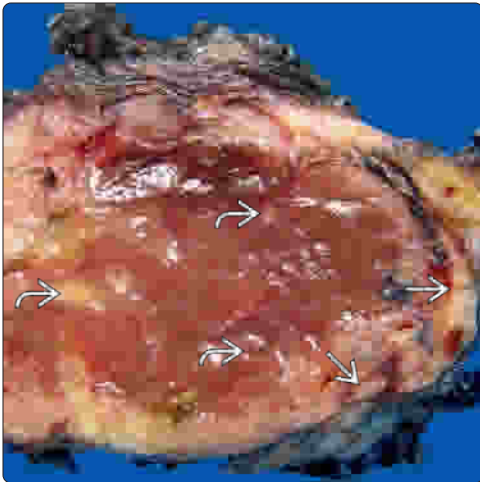
Clear Cell Tumors (If Clear Cell Oncocytoma)

- Clear cell mucoepidermoid carcinoma (MEC), epithelial-myoepithelial carcinoma (EMC), clear cell acinar cell adenocarcinoma, metastatic renal cell carcinoma (RCC)
 - All are malignant with infiltrative growth
 - None of these tumors tends to be completely composed of clear cells
 - Specific characteristics of each tumor help with separation
 - Epidermoid cells, mucocytes, and intermediate cells for MEC
 - Biphasic appearance of EMC
 - Basophilic cytoplasmic granules for acinar cell adenocarcinoma, lacking glycogen and PTAH reactions
 - Nuclear irregularities, prominent vascularity and extravasated erythrocytes, pax-8(+), CD10(+), RCC(+), and clinical history for RCC
- Clear cell myoepithelioma has myoepithelial markers by immunohistochemistry

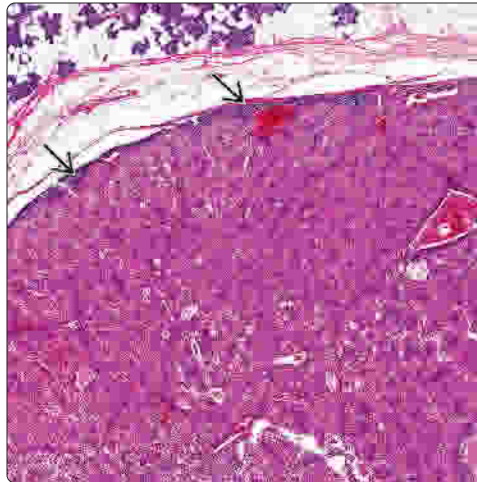
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Macroscopic Oncocytoma

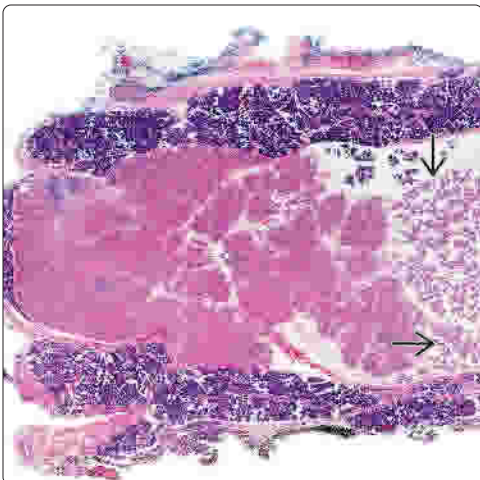


Capsule Around Oncocytoma

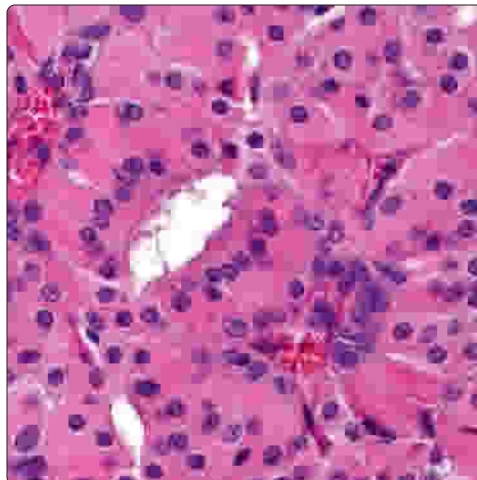


(Left) The parotid gland parenchyma at the periphery is compressed by the neoplasm. The cut surface is tan to reddish-brown, focally showing areas of degeneration or cystic change. The mahogany color is quite characteristic of oncocytoma. (Right) This well-circumscribed oncocytoma is distinctly separate from the salivary gland parenchyma. There is a very thin band of lymphocytes at the edge, an uncommon finding. There is a solid to glandular architecture.

Fatty Change in Oncocytoma

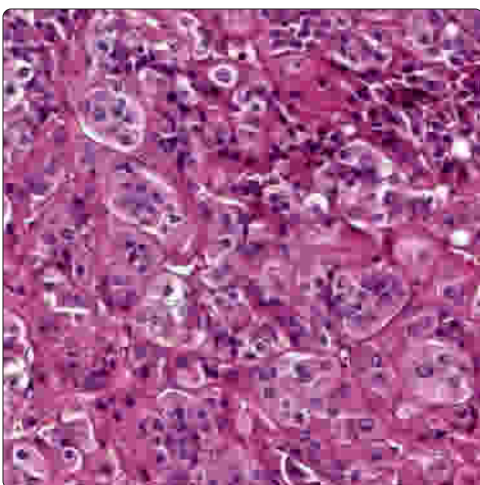


Oncocytes



(Left) The oncocytoma is composed of a dominant nodule within the parotid gland. However, areas of fatty change are noted within the tumor, creating a less cellular appearance. The tumor cells are oncocytes. (Right) A glandular or acinar appearance can be seen in this tumor composed exclusively of oncocytes. There is a lack of cytologic atypia, and the nuclei are round and regular.

Paraganglioma-Like Pattern



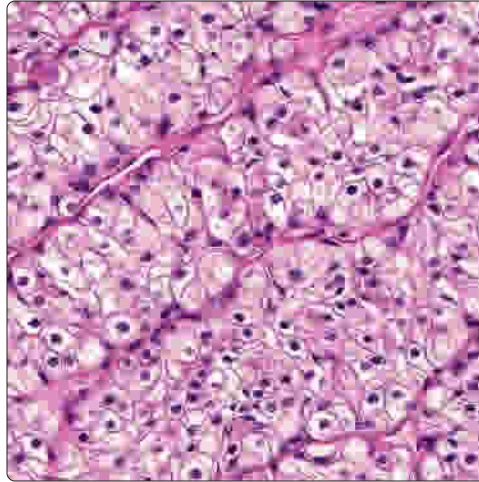
Cystic Change in Oncocytoma



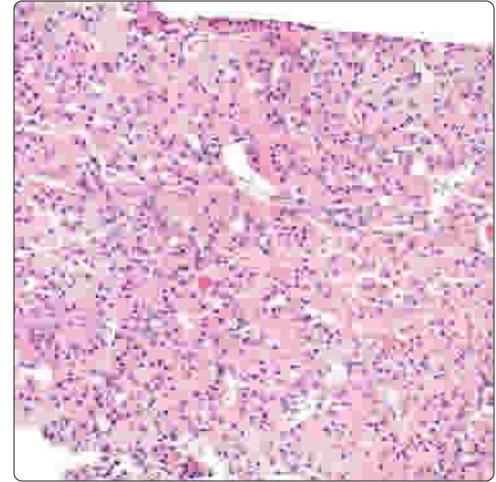
(Left) Oncocytoma may be arranged in a paraganglioma-like or zellballen architecture, as seen in this example. There are wisps of fibrous connective tissue. (Right) Oncocytoma may undergo cystic change. There is a flocculent-serous material within the cysts, lined by oncocytes. The cysts vary in size and shape. There is a generalized lack of lymphocytes, a helpful feature in differentiating oncocytoma from Warthin tumor.

(Left) A slight clearing of the cytoplasm can be seen in this oncocytoma. Note the very prominent cell borders. The very well-developed fibrovascular stroma separates the tumor cells into a trabecular architecture. **(Right)** A core needle biopsy is a common procedure in salivary gland tumors. While the features are quite classic and characteristic in this core needle biopsy, it is important to consider other tumor types and other nonneoplastic entities in the differential diagnosis.

Clear Cell Oncocytoma

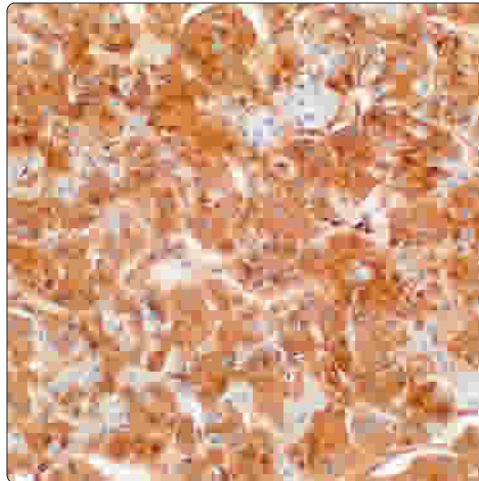


Core Needle of Oncocytoma Biopsy

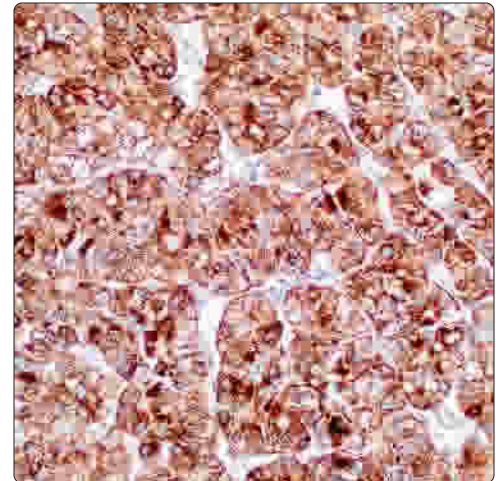


(Left) α -1-antitrypsin shows a strong and diffuse reaction in the cytoplasm of the neoplastic cells. This is not a specific or sensitive reaction, however. **(Right)** The cytoplasmic mitochondria show a very strong and diffuse granular reaction with SDHB in oncocytoma cells.

α -1-Antitrypsin Reaction

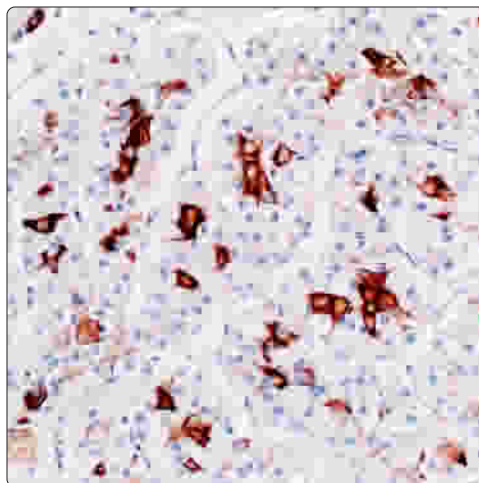


SDHB Granular Reaction

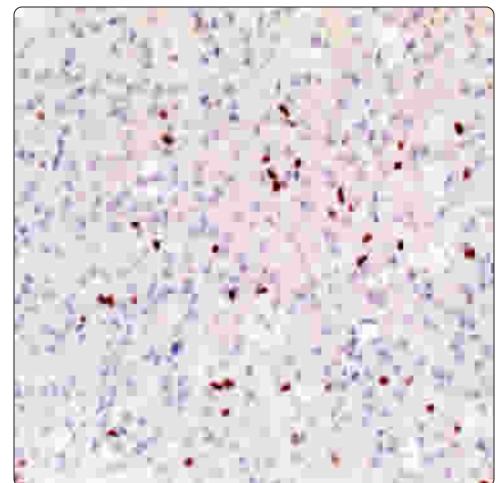


(Left) There is often biphasic staining with various markers in oncocytoma. In this case, there seems to be a luminal cell accentuation with CK7, different from the EMA or CK8/18 reaction. **(Right)** The majority of the neoplastic cells are negative with p63, although; isolated nuclei will be reactionary in a basal distribution.

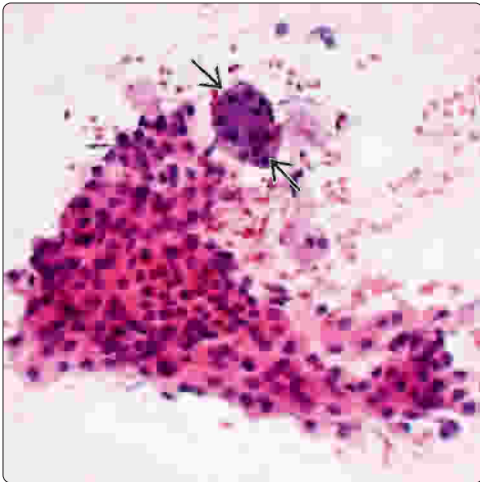
Central CK7 Reaction



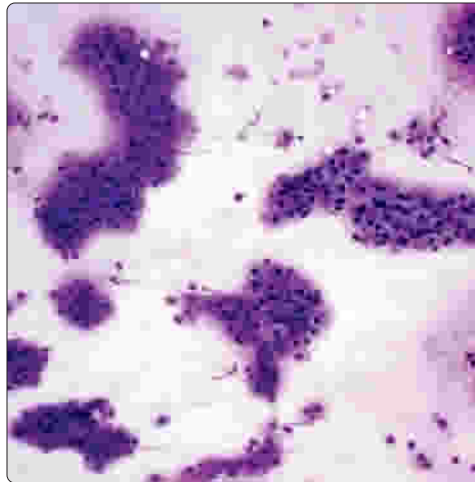
p63(+) Basal Cells



Cytology Smear of Oncocytoma

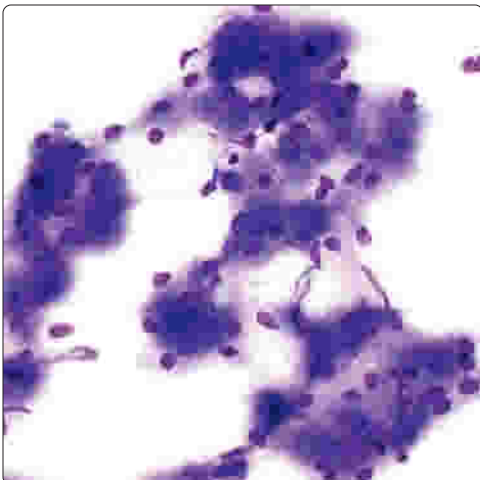


Clusters of Oncocytes

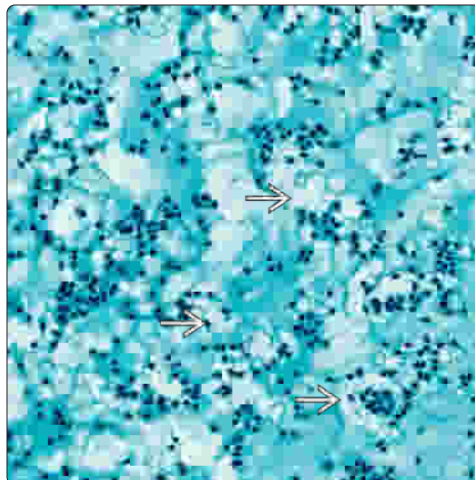


(Left) This smear demonstrates a sheet of oncocytic cells. There is slight overlapping with small, round, hyperchromatic nuclei identified. There is an acinus as a point of comparison to the oncocytic cells. Lymphocytes are absent from the background. (Right) Diff-Quik preparation stains the cytoplasm a dark purple-blue, creating a nearly opacified appearance. The cells are arranged in sheets and clusters, with some single cells. No lymphocytes are present.

Oncocytes

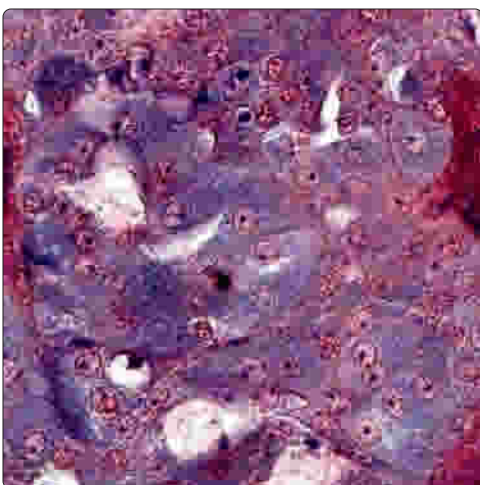


Clear Cell Oncocytoma

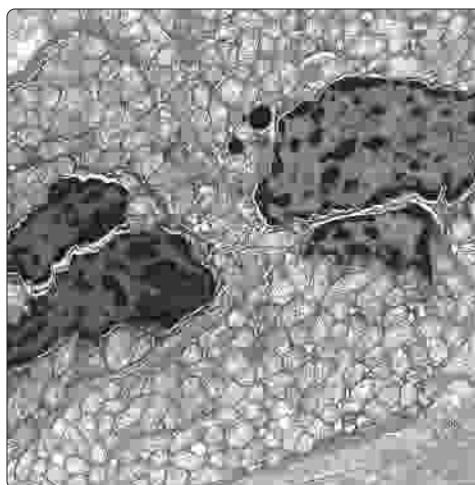


(Left) This Diff-Quik smear shows the purple appearance of oncocytes. There is abundant cytoplasm surrounding the round and regular nuclei. Note the lack of pleomorphism and lymphocytes. (Right) This clear cell oncocytoma FNA smear shows a very cellular aspirate. The clear cytoplasm creates a clearing in the background serum. The nuclei are small and round. The background lacks erythrocytes and lymphocytes, helping eliminate other tumors from the differential diagnosis.

PTAH Stains Mitochondria



Numerous Abnormal Mitochondria on EM



(Left) The PTAH stain accentuates the abnormal mitochondria by staining them as dark blue granules. This stain can be technically difficult to perform. (Right) The cytoplasm of this oncocyte is filled with round to oval to irregular-shaped mitochondria pushing against themselves and the nucleus. The mitochondria show abnormal, elongated cristae with a partial lamellar substructure. This electron microscopic appearance is characteristic for an oncocytoma. (Courtesy S. Bhuta, MD.)

Canalicular Adenoma

KEY FACTS

TERMINOLOGY

- Benign, epithelial salivary gland neoplasm arranged in interconnecting cords of columnar cells

CLINICAL ISSUES

- ~ 1% of all salivary gland tumors; 4% of all benign tumors
- Mean age: 67 years
- Female > male (1.7:1)
- Vast majority in **upper** lip
- Slowly enlarging mass
- Multifocality common (most common benign multifocal tumor)
- Conservative local excision, including multifocal tumors
 - Recurrences may represent incompletely excised &/or multifocal tumors

MACROSCOPIC

- Mean size: 1.6 cm

MICROSCOPIC

- Canalicular pattern with cords and ribbons showing connection points between opposing columnar cells within spaces
- Luminal squamous ball/morule
- Loose, fibrillar stroma; rich in hyaluronic acid and chondroitin sulphate
- Microliths (calcifications) may be seen

ANCILLARY TESTS

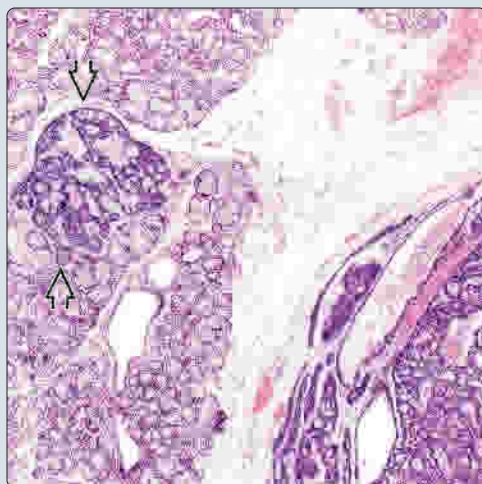
- **Positive:** AE1/AE3, CK7, S100 protein, SOX10, GFAP (periphery only)
- **Negative:** p63, p40, SMA, calponin, SMMHC
- Squamous morules: CK5/6, p16, and p63 (+)

TOP DIFFERENTIAL DIAGNOSES

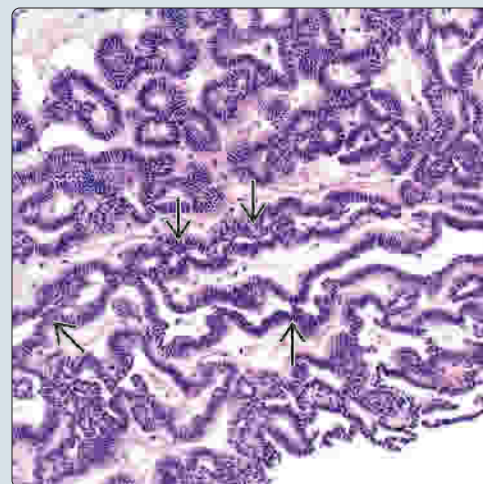
- Basal cell adenoma, pleomorphic adenoma
- Adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma

Multifocal Canalicular Adenoma

(Left) There is a topographically separate nodule from the main tumor mass in this example of tumor multifocality. There is an identical histologic appearance without any atypia. (Right) Canalicular architecture predominates in this tumor. Note the beading where the tumor cells touch one another in the middle of the canals.

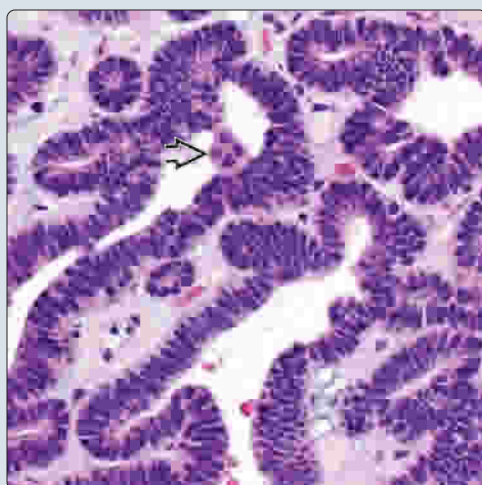


Beading of Tumor Cells

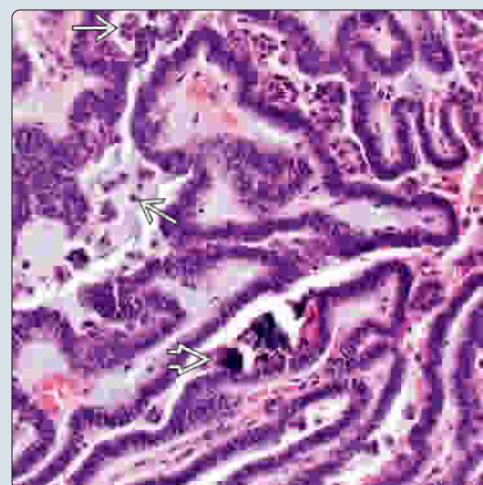


Intraluminal Squamous Morules

(Left) The tall columnar cells of the canalicular adenoma create canals. Within the lumen, isolated squamous morules (balls) are seen, which have a different immunohistochemistry than the surrounding neoplastic cells (CK5/6, p16 and p63 [+]). (Right) Numerous microliths (calcifications) are present without any adjacent necrosis or degeneration. Isolated squamous morules are present within the lumen of the canals.



Calcifications (Microliths)



TERMINOLOGY

Definitions

- Benign epithelial salivary gland neoplasm arranged in interconnecting cords of columnar cells

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon
 - 1% of all salivary gland tumors; 4% of all benign tumors
 - ~ 20% of all lip salivary gland tumors
- Age
 - Wide range: 33-91 years
 - Mean: 67 years
- Sex
 - Female > male (1.7:1)

Site

- Vast majority in **upper lip**
 - Buccal mucosa and palate infrequently affected

Presentation

- Symptom duration: Mean: 33 months
- Slowly enlarging mass
- Pain infrequently noted
- Mobile, compressible, frequently slightly blue, submucosal nodules
- Multifocality common

Treatment

- Surgical approaches
 - Conservative local excision, including multifocal tumors

Prognosis

- Excellent
 - Recurrences may represent incompletely excised &/or multifocal tumors

MACROSCOPIC

General Features

- Well circumscribed
- Light yellow/tan/brown nodules
- Cut surface frequently has cysts with gelatinous material

Sections to Be Submitted

- Include multifocal tumors, if present
- Borders with surrounding mucosa/stroma included

Size

- Range: 0.3-4 cm
- Mean: 1.6 cm

MICROSCOPIC

Histologic Features

- Well circumscribed, but bosselated or lobulated

- Most tumors are cystic
- Canalicular pattern with cords and ribbons showing connection points between opposing columnar cells within spaces
 - Beading: Columnar cells abutting one another within tubules
 - Luminal squamous ball/morule
- Tubules interconnect in lattice-like architecture
- Cuboidal to columnar basaloid cells
- Round to oval nuclei with scant, slightly eosinophilic cytoplasm
- Rare mitoses
- Loose, fibrillar stroma; rich in hyaluronic acid and chondroitin sulphate
- Histiocytes with lipofuscin pigmentation; foamy stromal histiocytes
- Luminal hemorrhage
- Microliths (calcifications) may be seen

Margins

- May be positive due to multifocality

ANCILLARY TESTS

Immunohistochemistry

- Unnecessary for diagnosis
- Various keratins are immunoreactive
 - Specifically: AE1/AE3, CK7, CAM5.2, 34βE12, EMA, CK19
- **Positive:** S100 protein, SOX10, CD117; GFAP (periphery)
- **Negative:** p63, p40, smooth muscle actin, calponin, SMMHC
- Squamous morules: CK5/6, p16, and p63 (+)

DIFFERENTIAL DIAGNOSIS

Basal Cell Adenoma

- Multiple patterns, without beading, basaloid cells only, no columnar cells, and characteristic collagenized stroma

Adenoid Cystic Carcinoma

- Linear arrangement of columnar cells is absent, with peg-shaped, angular, and irregular nuclei
- Infiltrative periphery with perineural invasion
- Reduplicated basement membrane

Pleomorphic Adenoma

- Not usually in canalicular pattern, contains myxochondroid matrix; strong reactions with basal-myoepithelial muscle markers

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Lymphadenoma and Sebaceous Lymphadenoma

KEY FACTS

TERMINOLOGY

- Sebaceous lymphadenoma (SLA)
 - Epithelial nests and cysts with focal sebaceous differentiation distributed within dense hyperplastic lymphoid tissue
- Lymphadenoma (LA) histologically similar yet devoid of sebaceous elements

CLINICAL ISSUES

- Average age: 6th-8th decades
- Equal gender distribution
- ~80% in parotid gland or surrounding tissues
- Conservative surgical excision is treatment of choice
- No recurrences reported following parotidectomy

MACROSCOPIC

- Solid and homogeneous to cystic, yellow to cream colored
- Size range: 1-6 cm

MICROSCOPIC

- Well circumscribed, partial to fully encapsulated
- Uniformly dense lymphoid component
- Evenly dispersed solid epithelial nests and cysts, with bland cytology
- Cysts of variable size
- SLA: Sebaceous cells in solid nests or within cyst walls
- LA: Lack of sebaceous component
- Foreign body reaction may be present due to cyst rupture

ANCILLARY TESTS

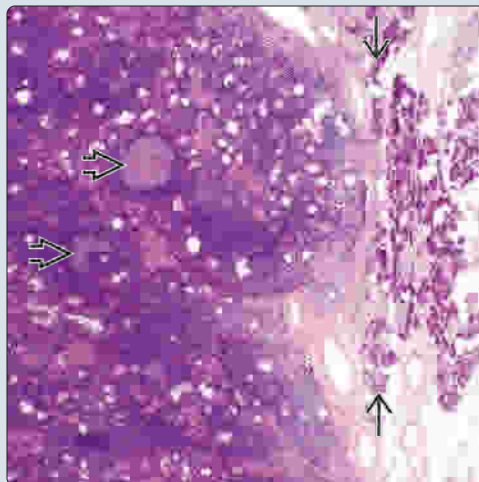
- p63, CK5/6 reactive in basal layer of sebaceous nests; BER-EP4(+) sebaceous cells

TOP DIFFERENTIAL DIAGNOSES

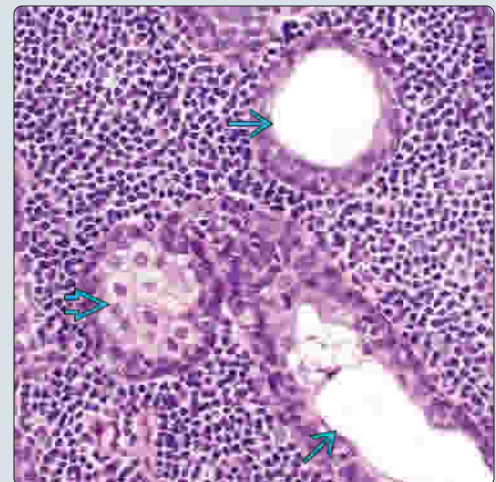
- Warthin tumor, tumor-associated lymphoid proliferation, metastatic carcinoma, pleomorphic adenoma

(Left) Sebaceous lymphadenoma (SL) demonstrates a pushing border into the parotid parenchyma [1]. Small cysts are present within a dense lymphoid stroma, which contains germinal centers [2]. **(Right)** SL demonstrates a small nest of sebaceous cells [3], variably sized cysts [4], and a dense lymphoid stroma. Sebaceous cells may also be seen within cyst walls.

Low Power of Sebaceous Lymphadenoma

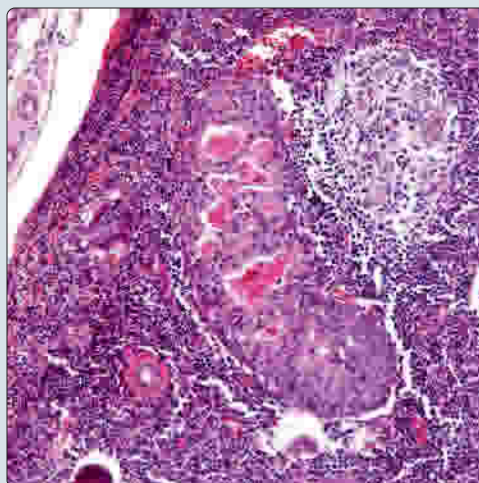


Sebocytes in Sebaceous Lymphadenoma

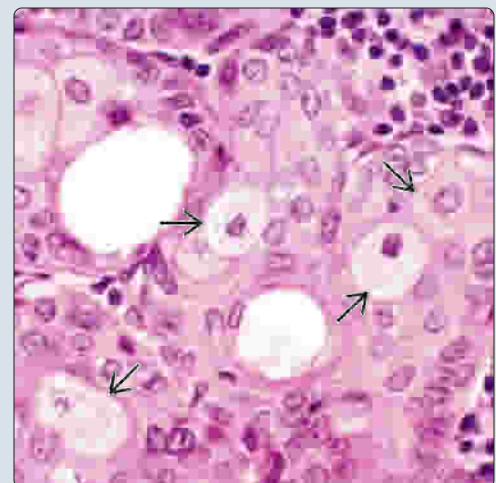


(Left) There is only a glandular epithelial component admixed with a very heavy inflammatory infiltrate in this encapsulated tumor, diagnosed as a lymphadenoma (LA). **(Right)** Well-differentiated sebaceous cells may be found in nests or in cyst walls [1]. Two small cystic spaces are evident.

Lymphadenoma With Epithelial Elements



Well-Developed Sebocytes



TERMINOLOGY

Abbreviations

- Sebaceous lymphadenoma (SLA)
- Lymphadenoma (LA)

Definitions

- **SLA**
 - Rare salivary gland neoplasm composed of epithelial nests and cysts with focal sebaceous differentiation distributed within dense hyperplastic lymphoid tissue
- **LA**
 - Histologically similar to SLA but devoid of sebaceous elements

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very rare
 - < 0.2% of all parotid gland neoplasms
- Age
 - Mean: 6th-8th decades; range: 11-79 years
- Sex
 - Equal gender distribution

Site

- ~ 80% in parotid gland or surrounding tissues
- Rare reports in minor salivary glands

Presentation

- Asymptomatic mass, present for 1 month-15 years
- Up to 30% have had immunosuppressive therapy for unrelated reasons

Treatment

- Conservative surgical excision

Prognosis

- No recurrences reported following adequate resection
- Rare malignant transformation

MACROSCOPIC

General Features

- Round to oval soft mass
- Solid and homogeneous to cystic
- Yellow to cream color

Size

- Range: 0.6-6 cm; median: 2.2 cm

MICROSCOPIC

Histologic Features

- Well circumscribed
 - Typically encapsulated
 - Pushing, yet noninfiltrative border
- Epithelial element
 - Evenly dispersed solid epithelial nests and cysts
 - Cysts of variable size
 - Squamoid, columnar, or cuboidal lining
 - May contain secreted material

- SLA: Sebaceous cells in solid nests or within cyst walls
- LA: Lack of sebaceous component
- Bland cytology
- Lymphoid component
 - Uniformly dense
 - Germinal centers may be focal to numerous
 - **No** infiltration/invasion of epithelial component
- Foreign body reaction may be present due to cyst rupture

ANCILLARY TESTS

Immunohistochemistry

- Pancytokeratin, CK5/6, CK7 reactivity in epithelial cells
- p63 reactive in basal layer of sebaceous nests; BER-EP4(+) sebaceous cells
- Lymphoid markers (CD3, CD20, Bcl-2, etc.) confirm reactive, hyperplastic lymphoid population
- **Negative:** HPV, EBV (EBER), HHV-8

DIFFERENTIAL DIAGNOSIS

Warthin Tumor

- Papillary cystic architectural pattern lined by bilayered oncocytic epithelium
- Sebaceous elements rare to nonexistent in Warthin tumor

Tumor-Associated Lymphoid Proliferation

- Reactive lymphoid infiltrate commonly seen associated with mucoepidermoid carcinoma and acinic cell adenocarcinoma
- Tumor-associated lymphoid proliferation (TALP) infiltrate poorly circumscribed and with variable density
- SLA and LA show well-defined borders and even lymphoid dispersion

Metastatic Carcinoma

- Sebaceous adenoma and LA may mimic metastatic disease to lymph nodes
- Bland cytology, even epithelial distribution, and relative morphologic consistency of nests and cysts favor SLA and LA

Pleomorphic Adenoma

- Usually does not have such heavy TALP-like growth; may have sebaceous cells occasionally; has myxochondroid matrix

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Sebaceous Adenoma

KEY FACTS

TERMINOLOGY

- Rare, benign salivary gland neoplasm composed of proliferating epithelial cells with focal sebaceous differentiation

CLINICAL ISSUES

- Most often in parotid gland
- Conservative yet total surgical excision
- No reports of recurrence or malignant degeneration

MICROSCOPIC

- Epithelial proliferation forming variably sized solid nests or cysts
- Well circumscribed with inconsistent encapsulation
- Peripheral epithelial cells are immature and surround variably mature sebaceous cells
- Quantity of well-differentiated sebaceous cells varies from minimal to abundant
- Squamous differentiation also observed

- Occasional oncocytes or mucocytes

ANCILLARY TESTS

- **Positive:** Pancytokeratin, epithelial membrane antigen;
- **negative:** Actin-sm, S100 protein

TOP DIFFERENTIAL DIAGNOSES

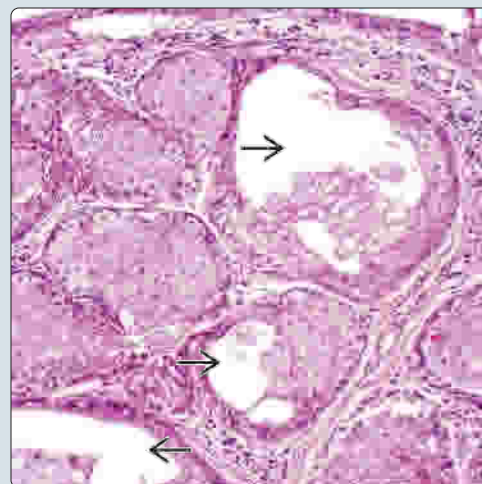
- **Mucoepidermoid carcinoma**
 - Nests with well-differentiated sebaceous cells are rare to nonexistent in mucoepidermoid carcinoma (MEC)
 - Clear cells and intermediate cells of MEC not seen in sebaceous adenoma
- **Sebaceous adenocarcinoma**
 - Other features of malignancy (necrosis, perineural invasion, or significant pleomorphism) not seen in sebaceous adenoma
- **Fordyce granules (sebaceous hyperplasia)**
 - Lobules in sebaceous hyperplasia are few in number and surround excretory duct

Sebaceous Adenoma With Capsule

(Left) Low-power view shows sebaceous adenoma. This predominantly solid example is well circumscribed and encapsulated [B]. Mainly cystic lesions may display an irregular interface with the surrounding parenchyma. **(Right)** In this sebaceous adenoma, variably sized and shaped nests of sebaceous cells show cystic degeneration [B]. Small primitive basaloid cells surround the periphery of the solid nests and cysts. The sebaceous cells have abundant vacuolated cytoplasm but no cytologic atypia is present.

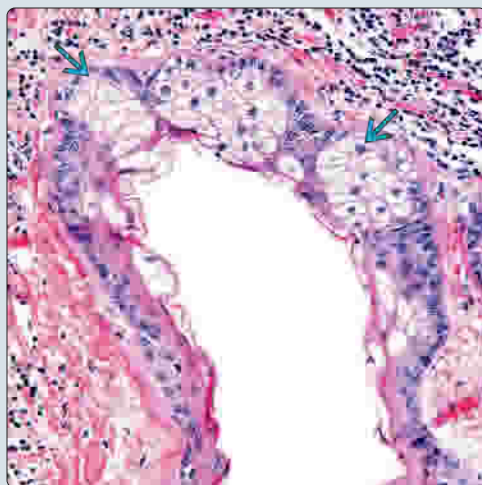


Cystic Change in Sebaceous Adenoma

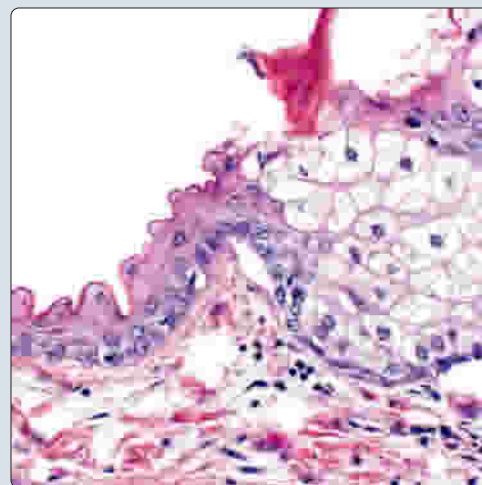


Sebocytes Within Cyst Wall

(Left) Sebaceous adenoma (cystic variant) is shown. Variably sized nests of sebaceous cells [B] are located within the wall of a cystic space lined by stratified squamous epithelium. Occasionally oncocytic metaplasia can be seen as well as histiocytes or foreign body-type giant cells. **(Right)** Sebaceous cells are shown within a squamous epithelial cyst wall. Note the corrugated squamous lining. Lymphoid follicles, necrosis, and mitoses are absent in sebaceous adenomas.



Squamous Cells and Sebocytes



TERMINOLOGY

Abbreviations

- Sebaceous adenoma (SA)

Definitions

- Rare, benign salivary gland neoplasm composed of proliferating epithelial cells with focal sebaceous differentiation

CLINICAL ISSUES

Epidemiology

- Incidence
 - < 1% of all salivary gland neoplasia
- Age
 - Wide age range: 22-90 years
 - Mainly adults: Average: 6th-7th decades
- Sex
 - Male > female (4:3)

Site

- Most often in parotid gland (48%)
 - Rare reports in submandibular gland (13%)
 - Intraoral tumors may be salivary gland origin or associated with Fordyce granules

Presentation

- Asymptomatic
- Firm, slowly growing mass

Treatment

- Conservative, yet total excision

Prognosis

- No reports of recurrence or malignant degeneration
- Unlike cutaneous SA, no reported association with Muir-Torre syndrome
 - Genodermatosis characterized by sebaceous neoplasms of skin and visceral malignancies (gastrointestinal or genitourinary carcinomas)

MACROSCOPIC

General Features

- Firm, well-circumscribed, pinkish, grayish white, or yellowish mass
- Solid or cystic

Size

- Range: 0.4-6.0 cm

MICROSCOPIC

Histologic Features

- Epithelial proliferation forming variably sized solid nests or cysts
- Well circumscribed with inconsistent encapsulation
 - Cystic areas may show haphazard boundary with surrounding parenchyma
- Peripheral epithelial cells are immature and surround variably developed sebaceous cells
 - Quantity of well-differentiated sebaceous cells varies from minimal to abundant

- Squamous differentiation usually observed
 - Especially identified lining cystic spaces
- Occasional oncocytes or mucocytes
 - Will be highlighted with PTAH or mucicarmine, respectively
 - Sebaceous cells will be nonreactive with these histochemical stains
- Foreign body reaction may be noted surrounding extravasated cystic material
- Lymphoid follicles, cytologic atypia, necrosis, and mitoses are usually not present in SA

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** Pancytokeratin, epithelial membrane antigen
- **Negative:** Actin-sm, S100 protein

DIFFERENTIAL DIAGNOSIS

Mucoepidermoid Carcinoma

- Focal mucocytes and squamous differentiation may suggest mucoepidermoid carcinoma (MEC)
- Sebaceous adenoma is usually circumscribed and noninfiltrative
- Nests with well-differentiated sebaceous cells are rare to nonexistent in MEC
- Although epidermoid cytomorphology is present, MEC lacks true squamous differentiation
- Clear cells and intermediate cells of MEC not seen in sebaceous adenoma

Sebaceous Adenocarcinoma

- Due to partial encapsulation, infiltration into surrounding parenchyma may be simulated, suggesting malignancy
- Sebaceous adenoma lacks significant mitotic activity
 - Aberrant, atypical mitoses are not found
- Other features of malignancy (necrosis, perineural invasion, or significant pleomorphism) not seen in sebaceous adenoma

Fordyce Granules (Sebaceous Hyperplasia)

- Lobules in sebaceous hyperplasia are few in number and surround excretory duct
- Sebaceous adenoma lacks presence of excretory duct and epithelial nests may number in hundreds

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Ductal Papillomas

KEY FACTS

TERMINOLOGY

- Group of uncommon benign epithelial salivary gland neoplasms with unique features that include
 - Sialadenoma papilliferum (SP)
 - Intraductal papilloma (IP)
 - Inverted ductal papilloma (IDP)

CLINICAL ISSUES

- SP: Palate most common site (> 80%), particularly junction of hard and soft palates
- IP, IDP: Lip and buccal most common sites of occurrence
- Conservative but complete surgical excision is treatment of choice and is curative for all ductal papillomas

MICROSCOPIC

- SP: Exophytic and endophytic proliferation of squamous and ductal epithelium
 - Papillary to verrucoid growth composed of stratified squamous epithelium with fibrovascular core

- Endophytic proliferation of ductal epithelium immediately subjacent to (and merging with) surface squamous epithelium
- IP: Unicystic cavity lined by cuboidal to columnar epithelial cells giving rise to papillary fronds filling cavity
 - Epithelial cells composed of 1 or 2 layers of cuboidal or columnar epithelium with eosinophilic cytoplasm
 - Mucocytes (goblet cells) admixed within ductal epithelium
- IDP: Unencapsulated but well-demarcated, endophytic basaloid and squamous/epidermoid cell growth
 - Composed of thick, bulbous proliferations contiguous with, but not protruding from, surface epithelium
 - Communication with surface by narrow opening may be seen

TOP DIFFERENTIAL DIAGNOSES

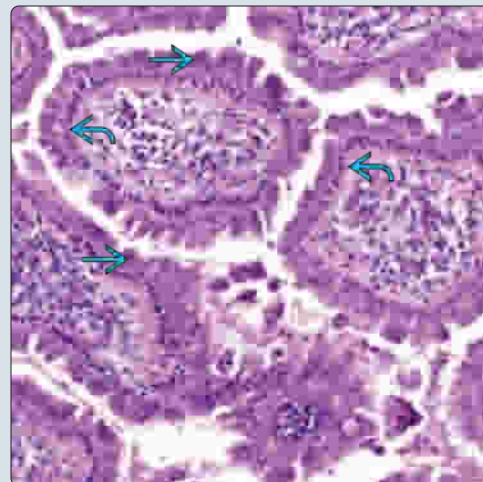
- Mucoepidermoid carcinoma, papillary cystadenoma, verrucous carcinoma

Sialadenoma Papilliferum

(Left) As seen here, sialadenoma papilliferum is characterized by an endophytic cavity of papillary (ductal) epithelium merging with surface squamous epithelium; abrupt transition from squamous epithelium to mucosal proliferation is present. (Right) Sialadenoma papilliferum is composed of an outer layer of columnar cells with an eosinophilic granular cytoplasm and an inner layer of cuboidal (basal) cells; the stroma includes many mature plasma cells.

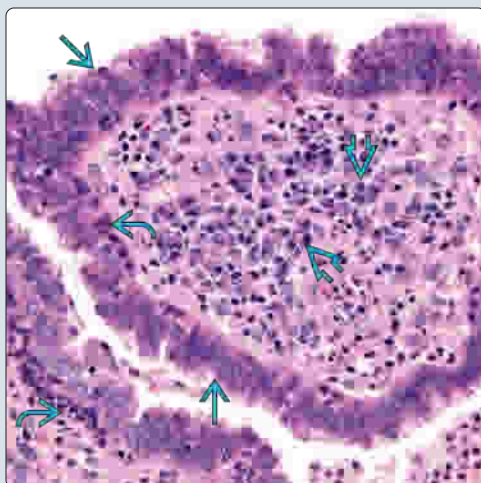


Sialadenoma Papilliferum



Sialadenoma Papilliferum

(Left) At higher magnification, the ductal epithelium includes an outer layer of columnar cells and an inner layer of cuboidal (basal) cells; the stroma includes an admixture of mature plasma cells and lymphocytes. (Right) In contrast to ductal papillomas, low-grade mucoepidermoid carcinoma (MEC) is comprised of an admixture of mucocytes, epidermoid cells, and intermediate cells. This combination of cell types is diagnostic for MEC even in the absence of invasion.



Mucoepidermoid Carcinoma, Low Grade



TERMINOLOGY

Abbreviations

- Sialadenoma papilliferum (SP)
- Inverted ductal papilloma (IDP)
- Intraductal papilloma (IP)

Synonyms

- Epidermoid papillary adenoma (for IDP)
 - IDP shares histologic features with sinonasal (schneiderian) inverted papilloma but does not share biologic behavior associated with sinonasal (schneiderian) inverted papilloma
- Called SP due to similarity with cutaneous syringocystadenoma papilliferum

Definitions

- Group of uncommon benign epithelial salivary gland neoplasms with unique histologic features that includes SP, IP, IDP
 - SP: Benign salivary gland tumor characterized by exophytic (papillary) and endophytic epithelial proliferation of mucosa or salivary duct origin
 - IP: Benign salivary gland neoplasm characterized by unicystic duct dilatation of luminal papillary proliferation arising from segment of interlobular or excretory duct
 - IDP: Benign salivary gland neoplasm characterized by
 - Luminal papillary projection arising at junction of salivary gland duct and oral mucosal surface epithelium with characteristic inverted (endophytic) growth

CLINICAL ISSUES

Epidemiology

- Incidence
 - SP, IP: Uncommon
 - IDP: Rare
- Age
 - SP, IDP: Occurs primarily in adults over wide range but is most frequent in 6th-7th decades
 - IP: Primarily affects adults in 4th-7th decades
- Sex
 - SP: Male > female
 - IDP, IP: Equal gender distribution

Site

- SP: Most common site of occurrence is palate (> 80%), particularly junction of hard and soft palates
 - Other minor salivary glands sites involved may include buccal mucosa, retromolar region, tonsillar pillar, lip, and nasopharynx (adenoids)
 - Major gland involvement rare; when involved, parotid gland most commonly affected
- IP: Intraoral minor salivary glands are most frequently involved
 - Buccal mucosa and lips most commonly affected
 - Other less common sites include floor of mouth, soft palate, and tongue
 - Involvement of major glands rare
- IDP: Most common sites of occurrence include lower lip and buccal (vestibular) mucosa

- Other sites of involvement include upper lip, floor of mouth, and soft palate

Presentation

- SP: Asymptomatic (painless) lesion generally discovered incidentally
 - Clinical appearance often mistaken for papilloma
 - Duration of symptoms may be from months to years
- IP: Painless mass
- IDP: Generally asymptomatic; may present as slow-growing painless, nodular submucosal swelling

Treatment

- Surgical approaches
 - SP, IP, IDP: Conservative, but complete surgical excision is treatment of choice

Prognosis

- SP, IP, IDP: Cured following complete excision
 - Recurrence rare
 - Malignant transformation of SP rarely occurs but not known to occur in IP, IDP

MACROSCOPIC

General Features

- SP: Well-circumscribed, papillary or verrucoid, round to oval, tan pink-appearing lesion
 - Base of lesion is broad or pedunculated
- IP: Well-circumscribed, mucosa-covered (nonulcerated) nodule
 - Cut section reveals unicystic lesion containing friable tissue
- IDP: Submucosal firm nodule
 - Small surface pore may be seen, which is contiguous with lumen of tumor

Size

- SP: Measures from few mm to as large as 7 cm
- IP: Measures from 0.5-2 cm in greatest dimension
- IDP: Measures up to 1.5 cm in greatest dimension

MICROSCOPIC

Histologic Features

- SP: Exophytic and endophytic proliferation of surface and ductal epithelium
 - Papillary to verrucoid growth composed of stratified squamous epithelium with fibrovascular connective tissue core
 - Acanthosis and parakeratosis of squamous epithelium seen
 - Endophytic proliferation of ductal epithelium is present, lying immediately subjacent to (and merging with) surface squamous epithelium
 - Abrupt transition from stratified squamous epithelium covering mucosal papillary proliferation to columnar epithelium lining ducts
 - Ductal epithelium unencapsulated, forming dilated and tortuous structures
 - Deeper portions of ductal structures have papillary luminal projections and microcysts

- Absence of encapsulation and presence of poor circumscription at base of lesion may simulate presence of invasive growth
- o Ductal epithelium composed of 2 cell layers
 - Outer or luminal layer composed of tall columnar cells with eosinophilic granular cytoplasm
 - Inner or basal cell composed of cuboidal cells with eosinophilic granular cytoplasm
- o Interspersed mucous cells and oncocytic cells may be seen
- o Chronic inflammatory cell infiltrate is predominantly plasma cells admixed with mature lymphocytes present in lamina propria of squamous component and in stroma of glandular component
- IP: Unicystic cavity lined by 1 or 2 layers of epithelial cells, giving rise to numerous papillary fronds with thin fibrovascular core filling cavity
 - o Epithelial cells composed of 1 or 2 layers of cuboidal or columnar epithelium with eosinophilic cytoplasm
 - Papillations are covered by similar epithelium
 - Cytologic atypia is absent with no significant increase in mitotic activity
 - Mucocytes, in form of goblet cells, seen admixed within ductal epithelium
 - o Continuity of papillary projections to cyst wall present, but depending on sections papillae may not be seen in continuity to cyst wall and appear to float within lumen
 - o Epithelial component confined to cyst cavity without extension into adjacent stromal tissue
- IDP: Unencapsulated but well-demarcated, endophytic epithelial growth
 - o Composed of thick, bulbous proliferations contiguous with, but not protruding from, surface epithelium
 - o Communication with surface by narrow opening may be seen
 - o Downward (endophytic) growth appears to fill luminal cavity
 - Endophytic growth is "pushing" into submucosa rather than demonstrating invasion or infiltration
 - o Consists of basaloid and squamous/epidermoid cells with interspersed mucous cells and microcytes
 - o Cytologic atypia is absent with no significant increase in mitotic activity
 - o Luminal surface epithelium composed of cuboidal or columnar cells with papillary appearance

ANCILLARY TESTS

Histochemistry

- Mucous cells: Intracytoplasmic mucicarmine and diastase-resistant, PAS(+) material

Immunohistochemistry

- SP
 - o Ductal luminal cells reactive for cytokeratins (AE1/AE3, CK7, CK19, CAM5.2), CEA, EMA, S100 protein
 - o Basal cells reactive for CK7, CK14, S100 protein, vimentin
 - o Langerhans cells S100 protein and CD1a **positive**

DIFFERENTIAL DIAGNOSIS

Mucoepidermoid Carcinoma (MEC)

- Characteristic cell types, including epidermoid cells, mucocytes, and intermediate cells, often with proliferative, thickened appearance are absent in SP, IP, IDP
- Presence of invasive tumor in MEC not feature of SP, IP, or IDP
 - o Diagnosis of MEC can be made in absence of invasive tumor only if requisite cell types (epidermoid cells, mucocytes, and intermediate cells) identified

Papillary Cystadenoma (PC)

- Possible differential diagnosis with IP; differentiating features include
 - o IP: Almost invariably unicystic lesion; PC: Most multicystic
 - o IP: Occurs in association with dilated salivary gland duct; PC: No association with salivary gland duct
 - o Intraluminal papillations of IP more complex and numerous than papillae of PC

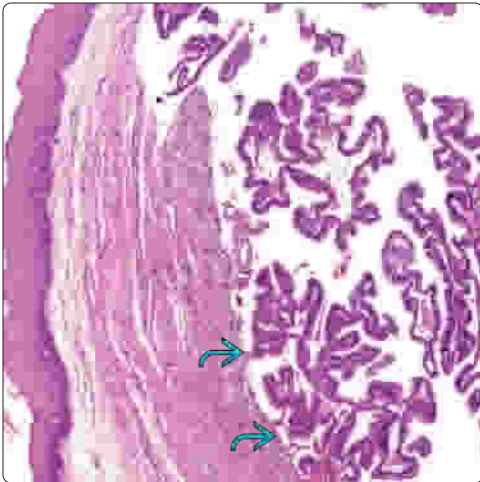
Verrucous Carcinoma (VC)

- Possible differential diagnosis with SP, differentiating features include
 - o Presence of tiered keratosis in VC absent in SP
 - o Absence of ductal component in VC present in SP

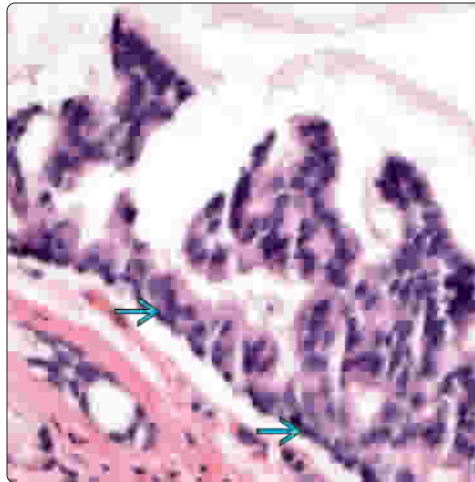
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Intraductal Papilloma



Intraductal Papilloma

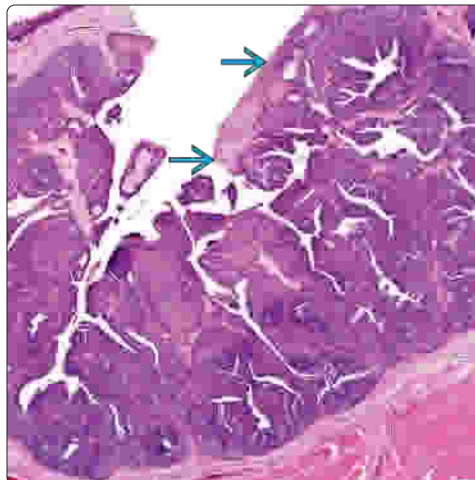


(Left) Intraductal papilloma is characterized by a submucosal circumscribed, unicystic epithelial-lined cavity giving rise to a papillary epithelial proliferation with fibrovascular cores filling the cystic cavity. (Right) At higher magnification, the cyst in the intraductal papilloma is lined by 1 or 2 layers of epithelial cells that give rise to an intracystic proliferation comprised of cuboidal to columnar epithelium with eosinophilic cytoplasm.

Intraductal Papilloma



Inverted Ductal Papilloma

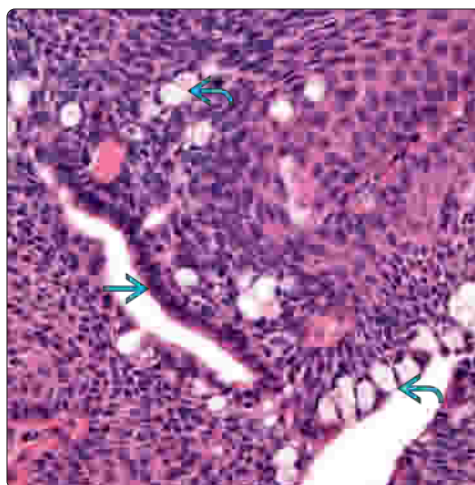


(Left) Another area of the intraductal papilloma shows the cyst lining cells and intracystic papillary structure to be comprised of cuboidal to columnar epithelium with eosinophilic cytoplasm. (Right) Inverted ductal papilloma appears as an unencapsulated but well-demarcated, endophytic epithelial growth composed of thick, bulbous proliferation contiguous with but not protruding from the surface epithelium. The downward (endophytic) growth appears to fill a luminal cavity.

Inverted Ductal Papilloma



Inverted Ductal Papilloma



(Left) Inverted ductal papilloma consists of a predominantly basaloid and squamous/epidermoid cell proliferation with interspersed mucous cells and luminal surface epithelium with cuboidal or columnar cells. (Right) At higher magnification, the predominant basaloid and squamous/epidermoid cell component is evident, lacking cytologic atypia and increased mitotic activity. Mucocytes and luminal surface cuboidal (or columnar cells) are also evident.

Cystadenoma

KEY FACTS

TERMINOLOGY

- Benign unicystic or multicystic epithelial neoplasm devoid of extraluminal solid growth

CLINICAL ISSUES

- Female > male (2-3:1)
- Wide range; average in 6th-7th decades
- Primary location in parotid gland (50%)
- When minor salivary glands are affected
 - Lips > buccal mucosa > palate
- Conservative surgical excision
- Recurrence uncommon after complete removal

MACROSCOPIC

- Single to multiple cystic spaces of variable size

MICROSCOPIC

- Well circumscribed but variable encapsulation
- Cystic spaces of variable number and size

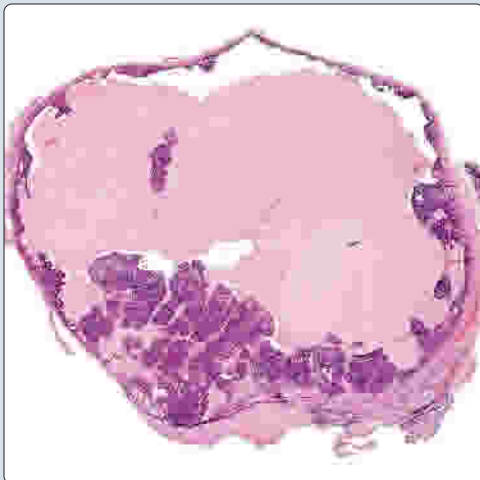
- Epithelial lining typically composed of cuboidal to columnar cells
- Intraluminal papillary proliferation may be evident
- Occasional mucinous or oncocytic epithelial lining, which may be focal or diffuse
- Bland cytology
- Rare mitotic figures
- **Papillary oncocytic cystadenoma**
 - Predominantly papillary with oncocytic epithelium

TOP DIFFERENTIAL DIAGNOSES

- Mucoepidermoid carcinoma
- Warthin tumor
- Cystadenocarcinoma
- Mammary analogue secretory carcinoma
- Salivary duct cyst

Cystadenoma

(Left) This cystadenoma shows a very well-circumscribed and encapsulated tumor. There are simple papillary projections into the lumen, which is filled with secretions. **(Right)** Relatively large cystic spaces containing a papillary intraluminal epithelial proliferation. The cysts are separated by fibrous connective tissue. There is no atypia, necrosis, or increased mitoses.



Complex Intraluminal Papillary Proliferation

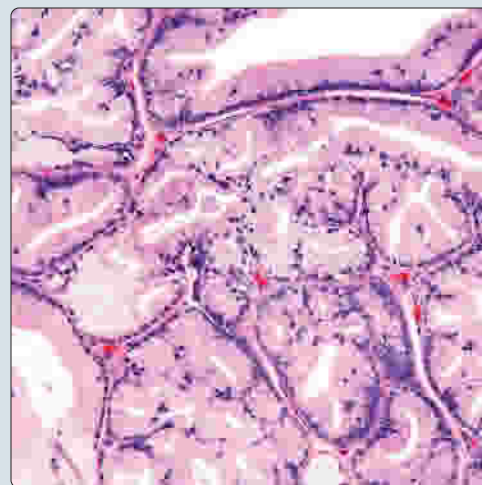


Oncocytic Papillary Cystadenoma

(Left) A papillary oncocytic cystadenoma demonstrates intraluminal papillary projections composed of bilayered oncocytic epithelium, similar to a Warthin tumor, however, a lymphoid infiltrate is absent or very scant. **(Right)** A cystadenoma composed of tall columnar mucocytes is shown. This rare form has been termed mucinous cystadenoma or cystadenoma, mucous cell type.



Mucocytes in Cystadenoma



TERMINOLOGY

Synonyms

- Cystic duct adenoma
- Papillary oncocytic cystadenoma

Definitions

- Benign unicystic or multicystic epithelial neoplasm devoid of extraluminal solid growth

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~ 4% of all benign epithelial salivary gland neoplasms
 - Roughly 10% of all minor salivary gland tumors
- Age
 - Wide range; average in 6th-7th decades
- Sex
 - Female > male (2-3:1)

Site

- Location and relative frequency vary depending upon study
- Parotid gland affected in ~ 50% of cases
- Minor salivary glands next most common
 - Lips > buccal mucosa > palate
- Occasional submandibular gland involvement

Presentation

- Slowly growing painless mass
- Mucosal lesions may simulate mucoceles

Treatment

- Conservative surgical excision

Prognosis

- Recurrence uncommon after complete removal
- Rare malignant transformation

MACROSCOPIC

General Features

- Single to multiple cystic spaces of variable size
- Possible intraluminal proliferation

MICROSCOPIC

Histologic Features

- Well circumscribed but variable encapsulation
 - Possible irregular interface with surrounding parenchyma
 - Cysts separated by fibrous connective tissue
 - Focal to spotty inflammatory element may be present in connective tissues
- Cystic spaces of variable number and size
 - Cysts may contain eosinophilic fluid &/or scattered detached cells
- Epithelial lining typically composed of cuboidal to columnar cells
 - Occasional mucinous or oncocytic epithelial lining, which may be focal or diffuse
 - Squamoid lining rare and typically focal
- Intraluminal papillary proliferation may be evident

- Especially common in unicystic lesions
- **Papillary oncocytic cystadenoma**
 - Cystadenoma with significant intraluminal papillary projections surfaced by single or bilayered oncocytic epithelial lining
 - Epithelial component may resemble Warthin tumor
- Bland cytology with rare mitotic figures
- Extraluminal solid growth is not typical
 - Presence should raise suspicion for malignancy, especially if abnormal cytology evident

DIFFERENTIAL DIAGNOSIS

Mucoepidermoid Carcinoma

- May contain significant cystic component and papillary growth
- Features include infiltrative border, extraluminal solid growth of epidermoid, intermediate, &/or clear cells

Warthin Tumor (Papillary Cystadenoma Lymphomatosum)

- Multiple cystic spaces lined by bilayered oncocytic epithelium
- Prominent dense lymphoid stroma, including germinal centers

Cystadenocarcinoma

- Malignancy in cystadenocarcinoma defined by frank invasion and pleomorphism
- Cystadenoma and low-grade cystadenocarcinoma may be cytologically and architecturally similar

Mammary Analogue Secretory Carcinoma

- Cystic change, but with vacuolated cytoplasm, scalloped secretions, papillary, acinar and solid patterns
- **Positive:** Mammaglobin, S100 protein, CK7, MUC4, and STAT5; *ETV6* by FISH

Salivary Duct Cyst

- Composed of markedly dilated salivary gland (parotid) duct, unicystic, with flattened epithelial lining surrounded by dense fibrous connective tissue
- Cystadenoma favored if intraluminal epithelial proliferation present

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Hemangioma

KEY FACTS

TERMINOLOGY

- Tumor composed of proliferation of endothelial cells forming variably mature blood vessels
 - Capillary (juvenile) hemangioma is most common

CLINICAL ISSUES

- 90% diagnosed in first 2 decades (neonatal period)
- Female >> male (2-4:1)
- Parotid gland is most common location (~90%)
 - Up to 25% are bilateral
- Gives bluish discoloration of overlying skin, especially when baby cries
- May show rapid enlargement during proliferative phase, involving adjacent structures
- Can be managed by observation, pharmacologic therapy, &/or surgery
- Majority spontaneously involute before 7 years (75-95%), many earlier
- Pharmacological therapy yields excellent response

IMAGING

- US favored because lesions are cystic, showing vascularity by color Doppler imaging
- MR shows strong enhancement with gadolinium

MICROSCOPIC

- Diffuse gland enlargement, with lobular expansion
- Gland replaced by closely packed endothelial cells and small immature capillaries, leaving ducts intact
- Variably sized and shaped vessels
- Mitoses often increased but never atypical
- **Cavernous** hemangioma: Large, expanding, cystic cavities, filled with blood

ANCILLARY TESTS

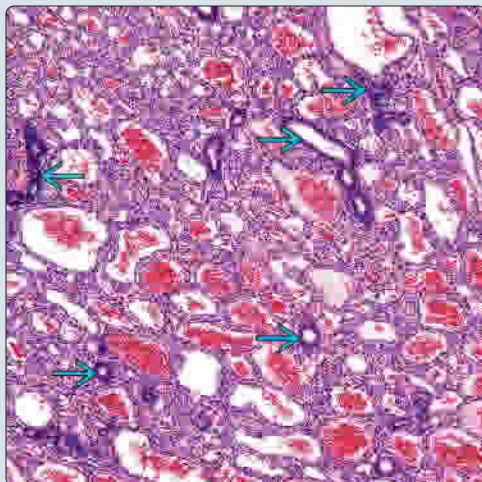
- Endothelial cells **positive**: CD31, CD34, FVIIIIRAg

TOP DIFFERENTIAL DIAGNOSES

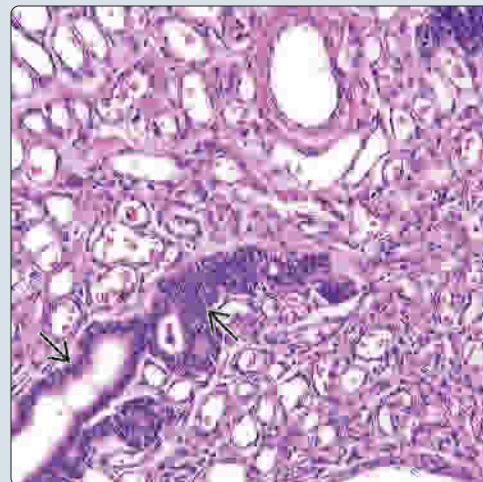
- Angiosarcoma, Kaposi sarcoma, phleboliths and angiolithiasis

(Left) A juvenile capillary hemangioma shows salivary gland ducts associated with innumerable endothelial-lined vascular spaces. The duct architecture is intact, but the glandular tissue is replaced. **(Right)** An excretory duct of the parotid gland is almost completely surrounded by a vascular proliferation. There are extravasated erythrocytes in the lumen. There is no atypia or anastomosing spaces.

Capillary Hemangioma Between Ducts

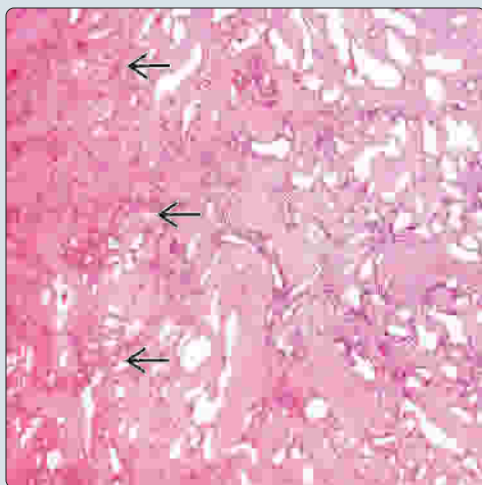


Capillary Hemangioma Channels

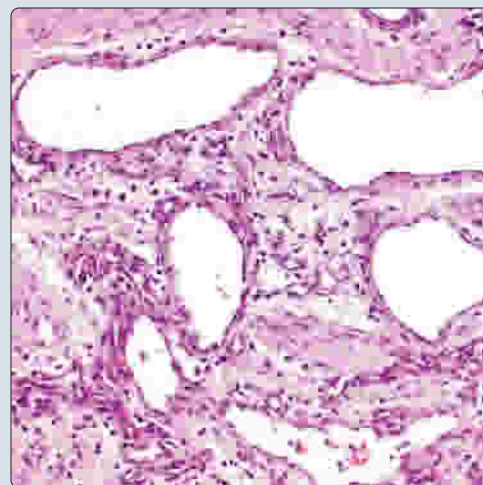


(Left) On H&E, residual salivary gland is noted, although the vascular channels in this hemangioma are accompanied by more fibrosis. This is a tumor that has started to involute. Dilated vascular spaces are easily identified. **(Right)** There are separated endothelial lined spaces in this example of a salivary gland hemangioma. The size of the vessels suggests this is a cavernous type.

Dilated Vascular Channels



Hemangioma Dilated Spaces



TERMINOLOGY

Synonyms

- Juvenile hemangioma
- Infantile hemangioma

Definitions

- Tumor composed of proliferation of endothelial cells forming variably mature blood vessels
 - All histologic variants of hemangioma occur in salivary glands, but capillary (juvenile) hemangioma is most common

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare: < 0.5% of salivary gland tumors
- Age
 - Majority (up to 90%) diagnosed in first 2 decades, highest in neonatal period
 - > 90% of parotid gland tumors in infants < 1 year are hemangioma
 - Cavernous hemangioma: Usually seen in adolescents or adults
- Sex
 - Female > > male (2-4:1)
 - **Capillary (juvenile)** hemangioma shows this ratio
 - **Cavernous** hemangioma tends to be seen more frequently in older male patients

Site

- Parotid gland is most common location (~ 90%)
 - Very rare in submandibular, sublingual, or minor salivary glands
- Up to 25% are bilateral

Presentation

- Usually asymptomatic soft tissue parotid swelling
- Arc of development is seen
 - Small swelling few weeks after birth
 - 1/2 of patients have cutaneous lesion at birth, yielding bluish discoloration of overlying skin
 - Accentuated when infant cries (baby becomes hypoxemic, so blue appearance is highlighted)
 - Mass detected by 6 months
 - Often shows rapid enlargement
 - During proliferative phase, 50-60% show skin ulceration
 - Overlying skin is usually not directly affected, but hemangioma "pushes" up
 - Facial asymmetry and deformity may be present
 - Sometime after 1st year, slow regression (involution) begins
 - May take years to completely involute (into teens): Very slow involutional phase
- Frequently, hemangiomas become large and involve adjacent structures
 - Ear, hypopharynx, parapharyngeal space, base of skull, subglottis, lip, eye, nose
- Pain and tenderness are not typical

- Consumptive coagulopathy (Kasabach-Merritt syndrome) **not** associated with salivary gland hemangiomas
- Rarely, may have "turkey wattle" sign: Enlargement of facial mass on dependency of head
 - Considered pathognomonic of vascular malformation or hemangioma

Treatment

- Options, risks, complications
 - Can be managed by observation, pharmacologic therapy, &/or surgery
 - Delay any definitive treatment in hope of spontaneous resolution
 - Biologically benign but occasionally associated with extensive and life-threatening growth
 - Uncommonly: Tracheostomy for airway compromise; congestive heart failure due to shunting
 - Complications may include: Cutaneous ulceration, bleeding, failure to thrive, scarring, facial nerve injury (during surgery), facial deformity, and death
- Surgical approaches
 - Early cosmetic resection can cure disfiguring tumors
 - Cavernous hemangiomas in adults should be excised (do not spontaneously involute)
 - Reconstructive procedure may be necessary after involution or pharmacologic therapy
- Drugs
 - Pharmacological therapy (corticosteroids and interferon) yields response in up to 98% of cases
 - May take several years to completely involute/resolve/regress
 - Corticosteroids result in regression or stabilization in about 80%
 - Interferon-α 2a or 2b gives additional regression in corticosteroid-resistant cases (95% of cases)
- Other
 - Laser (thermocautery) and radiotherapy only employed in rare, life-threatening cases
 - Pressure (compression) therapy or embolization if tumor is large

Prognosis

- Pediatric tumors initially grow rapidly, but vast majority involute
 - Majority spontaneously involute before age 7 (75-95%)
- Very rare malignant transformation to angiosarcoma

IMAGING

Radiographic Findings

- US favored as initial imaging study because lesions are cystic
 - Vascular lesions can be demonstrated with color Doppler imaging
- Tc-99m-labeled red blood cell scintigraphy can be used

MR Findings

- T2WI: Masses are hyperintense with numerous small vessels
- Strong enhancement with gadolinium

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CD34	Positive	Cytoplasmic	
CD31	Positive	Cytoplasmic	
FVIIIIRAg	Positive	Cytoplasmic	
FLI-1	Positive	Nuclear	
GLUT1	Positive	Nuclear	In juvenile type
D2-40	Negative		Reacts principally with lymphatic endothelial cells

MACROSCOPIC

General Features

- Diffuse gland enlargement, with expansion of lobules, lacking distinct tumor mass
- Hemorrhagic, red to brown

Size

- Frequently large (up to 10 cm)

MICROSCOPIC

Histologic Features

- Separated into hemangioma (> 90%) and lymphangioma (< 10%) (not considered here)
- Hemangiomas divided into juvenile (infantile) capillary hemangioma, cavernous hemangioma, and arteriovenous malformation (latter not further considered)

Juvenile (Infantile) Capillary Hemangioma

- Lobular architecture of gland is intact, separated by septa, but lobules are enlarged
- Salivary acini diffusely replaced by endothelial cells and small immature capillaries
 - Salivary gland ducts stand out, surrounded by proliferation
 - Peripheral nerves are not involved
- Closely packed sheets of endothelial cells and pericytes
- Vascular differentiation may be limited to small, inconspicuous lumina
 - During arc of development, lumina become dominant feature
- Variably sized and shaped vessels
 - Small capillary channels lined by plump, round to ovoid endothelial cells
 - Indistinct cell borders, oval nuclei, occasional groove, and small nucleoli
 - Larger, thin-walled vessels often accentuated at tumor periphery
- Mitoses often increased but **never** atypical
- Diffuse interstitial fibrosis and infarction seen in regression
 - Thrombi and phleboliths may be present

Cavernous Hemangioma

- Large, expanding, cystic cavities, filled with blood
- Expanded and compressed parotid parenchyma at periphery
 - Lacks retained salivary gland ducts
- Lined by plump to flattened endothelial cells

ANCILLARY TESTS

Cytology

- Usually **not** performed because there is high index of clinical accuracy and desire to avoid bleeding
- Bloody aspirates with groups and clusters of spindle-shaped cells and bland endothelial cells
 - Cells have limited cytoplasm and oval nuclei
- Isolated ductal structures may be noted

Histochemistry

- Reticulin highlights small fibers encircling vessels

Immunohistochemistry

- Endothelial cells **positive** for vascular markers

DIFFERENTIAL DIAGNOSIS

Angiosarcoma

- Exceedingly rare in age group affected by hemangioma
- Freely anastomosing vascular channels, pleomorphic cells, increased mitoses, atypical mitoses, necrosis, invasion, and destructive growth (glandular architecture destroyed)

Kaposi Sarcoma

- Seen in AIDS, male patients predominantly, and older age at presentation
- Involves submandibular or parotid gland, showing spindle cell vascular proliferation arranged in fasciculated bundles, variable nuclear pleomorphism, mitotic figures, extravasated erythrocytes, and hyaline globules
- **Positive:** Human herpesvirus 8

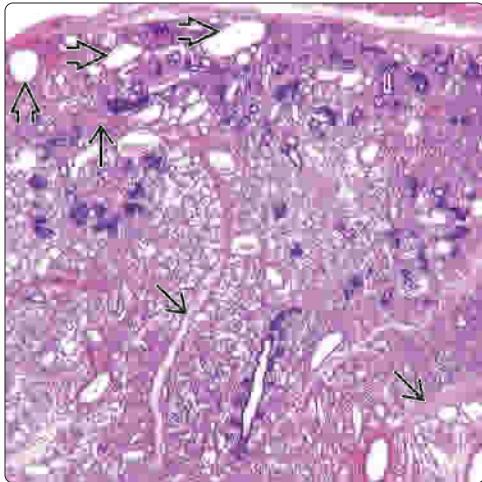
Phleboliths and Angiolithiasis

- May mimic sialoliths, although exceedingly uncommon in young patients
- Angiolithiasis are structures showing laminations of alternating low and high mineral content (apatite) associated with blood and fibroblasts

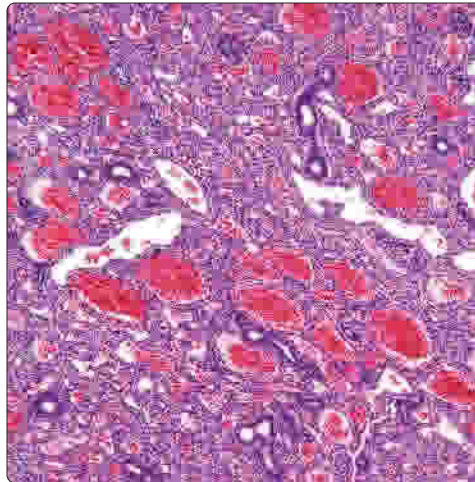
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Replacement of Parenchyma



Blood-Filled Spaces in Hemangioma

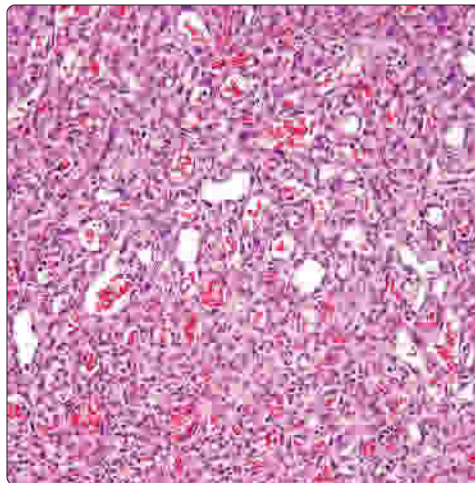


(Left) On low power, the dark purple residual salivary gland ducts stand out against the background of the vascular proliferation. Fibrous septa are easily identified. The vascular spaces are variably sized, with larger vessels noted at the periphery. **(Right)** An intermediate magnification shows large vessels filled with erythrocytes. Some of the vessels are empty. Note the more solid proliferation of vessels in the background. The ducts (dark purple) are not destroyed.

Slit-Like Vascular Channels

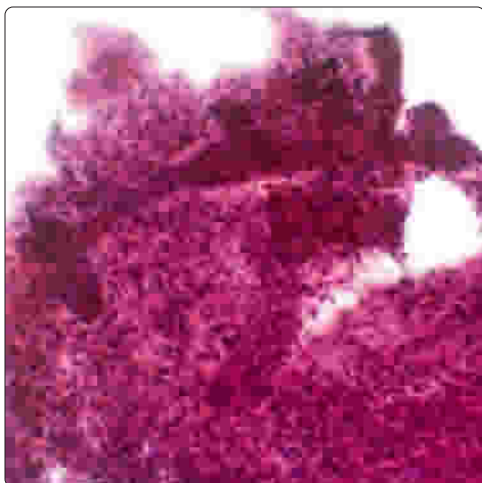


Capillary-Sized Vessels in Hemangioma

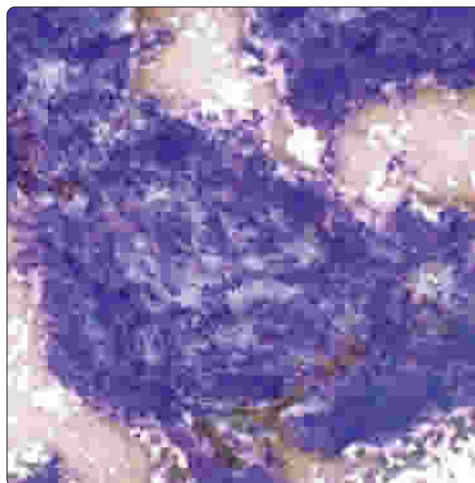


(Left) A highly cellular proliferation replaces the salivary gland acini in this case. Isolated ducts are noted. Small slit-like spaces hint at the vascular nature of the lesion. However, the majority of this lesion is comprised of immature vascular channels and endothelial cells. **(Right)** Numerous capillary-sized vessels are lined by unremarkable endothelial cells. Erythrocytes are noted within the lumen of many of the vessels. There is no atypia.

FNA With Spindled Neoplastic Cells



FNA of Hemangioma



(Left) There is a 3D cluster of spindle-shaped cells with bland endothelial cells comprising the biopsy. Blood was noted in the background, although absent in this field (alcohol fixed, Papanicolaou stained). **(Right)** A bloody background is noted with groups and clusters of spindle-shaped cells and bland endothelial cells, creating a network of vascular channels. Glandular epithelium is absent (air dried, Diff-Quik stained).

Sialoblastoma

KEY FACTS

TERMINOLOGY

- Sialoblastoma is low-grade, malignant epithelial, and myoepithelial neoplasm recapitulating primitive salivary gland anlage

CLINICAL ISSUES

- Extremely rare congenital tumor (< 50 case reports)
- Age: Prenatal, perinatal, to neonatal period
- Equal gender distribution
- Site: Parotid > submandibular gland (3:1)
- Rapid growth is common
- Complete surgical excision, possible chemotherapy or radiation
- Biologic behavior is unpredictable and variable

MICROSCOPIC

- Size range: 2-15 cm
- Patterns of growth include
 - Solid nests, cribriform, trabeculae, nodules

- Basaloid epithelial cells with scanty cytoplasm
 - Oval nuclei, single nucleoli, fine chromatin
- More mature cuboidal cells forming ductules
- Mitoses are usually easy to find
- Necrosis (comedonecrosis) can be detected



ANCILLARY TESTS

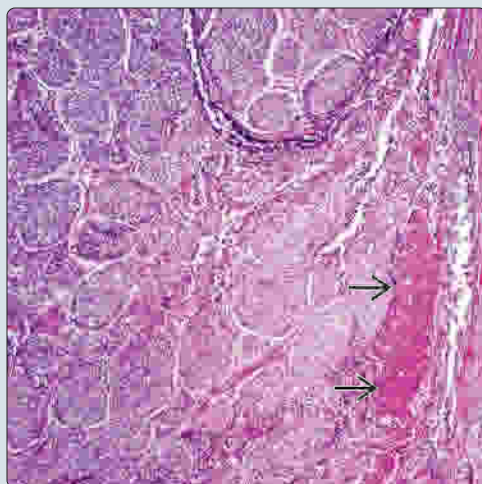
- Biphasic immunohistochemistry for ductal and basaloid cells
 - Ductal cells: Cytokeratin, CK7, CK19
 - Basaloid/myoepithelial cells: S100 protein, actin, calponin, p63
- p53 overexpressed in tumors with more aggressive biologic behavior

TOP DIFFERENTIAL DIAGNOSES

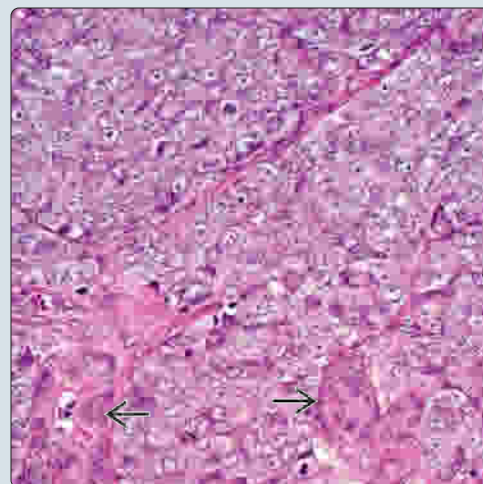
- **Benign:** Pleomorphic adenoma, basal cell adenoma, teratoma
- **Malignant:** Adenoid cystic carcinoma

Lobular Architecture With Necrosis



(Left) The tumor shows a lobular architecture with a slight cracking artifact around the lobules. An area of comedonecrosis  is present within the tumor trabeculae. **(Right)** There is a syncytial arrangement of these basaloid cells showing vesicular to delicate nuclear chromatin. Small duct-like cuboidal cells  are noted within the tumor. Mitoses are easily identified.

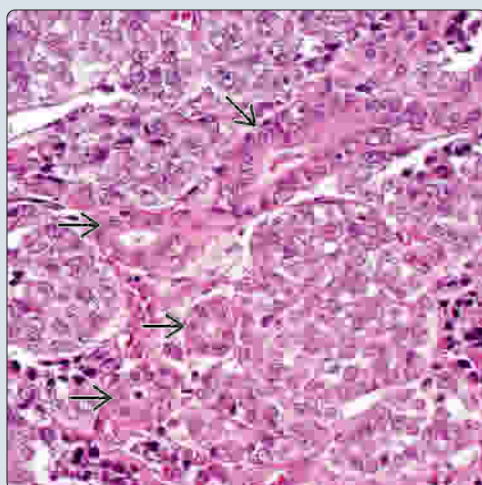


Syncytial Architecture of Basaloid Cells

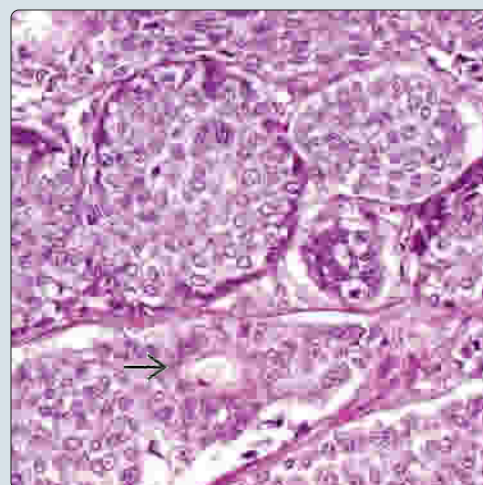


Mature Cuboidal Cells

(Left) This image highlights the biphasic appearance of the tumor. There are nests of basaloid cells juxtaposed with more mature cuboidal cells, which are forming ductules . A hint of palisading is noted. **(Right)** Nests and lobules of cells can be seen in a sialoblastoma. Focal areas show more mature cuboidal cells creating a gland . There is usually a single nucleolus with a gossamer-fine chromatin pattern.



Focal Cuboidal Cells



TERMINOLOGY

Synonyms

- Congenital basal cell adenoma
- Embryoma
- Congenital hybrid basal cell adenoma-adenoid cystic carcinoma
- Basaloid adenocarcinoma

Definitions

- Sialoblastoma is low-grade, malignant epithelial, and myoepithelial neoplasm recapitulating primitive salivary gland anlage

ETIOLOGY/PATHOGENESIS

Reserve Cell Origin

- May arise from retained blastema cells
 - Dysembryogenic changes in parenchyma adjacent to tumor
 - Focal proliferation of terminal ductal epithelial bulbs
 - Salivary anlage at arrested state of differentiation
- May arise from basal reserve cells

CLINICAL ISSUES

Epidemiology

- Incidence
 - Extremely rare congenital tumor (< 50 case reports)
- Age
 - Prenatal, perinatal, to neonatal period (60% < 10 days old)
 - Very rare after 2 years
- Sex
 - Equal gender distribution

Site

- Parotid > submandibular gland (3:1)

Presentation

- Parotid or submandibular gland region
- If tumors are large, skin ulceration may be seen
- Rapid growth is common
- Preoperative core-needle biopsy helps to exclude other lesions that require different management
- Infrequently associated with *nevus sebaceus* and hepatoblastoma (elevated α -fetoprotein)
 - Also considered congenital lesions

Treatment

- Complete surgical excision is treatment of choice
- Radiation may be used, but complications hamper use in very young
- Chemotherapy has untoward long-term sequelae, especially in patients so young
 - If primary tumor is unresectable, consider chemotherapy

Prognosis

- Biologic behavior is unpredictable and variable
 - Tumor may be benign, indolent, or aggressive
- In **most** patients, surgery is curative
- Recurrences develop in up to 21% of all patients
 - Usually manifests within 24 months of diagnosis

- Regional metastases may be seen in up to 10%
- Distant metastases uncommon (9%): Lung
- Aggressive clinical course suggested by unfavorable histology (4% die of disease)
 - Perineural &/or vascular invasion, necrosis, significant pleomorphism

IMAGING

Radiographic Findings

- Prenatal sonography may identify expansile, large, lobulated mass
- Hemorrhage and necrosis may be useful findings

MACROSCOPIC

General Features

- Lobular, multinodular, partially circumscribed mass
- Gray, yellow, or white
- Focal necrosis and hemorrhage may be present

Size

- Range: 2-15 cm

MICROSCOPIC

Histologic Features

- Approximately recapitulates embryologic development of salivary glands at 3rd month
- 2 major patterns of growth, prognostically significant
 - **Favorable pattern**
 - Partial encapsulation
 - Bland basaloid tumor cells with intervening stroma
 - **Unfavorable pattern**
 - Broad pushing to infiltrative borders
 - Perineural or vascular invasion
 - Anaplastic basaloid tumor cells with scant stroma
 - Tumor necrosis
- Patterns of growth include
 - Solid nests, cribriform, trabeculae, or nodules with peripheral palisading
- Basaloid epithelial cells with scanty cytoplasm
- Round to oval nuclei
 - Usually single nucleolus with gossamer-fine chromatin pattern
 - Multiple nucleoli can be seen
- More mature cuboidal cells forming ductules are sometimes seen
 - Peripheral palisading can be present
- Nuclear pleomorphism can be focally recognized
- Stroma is usually loose, immature, and myxoid
- Myoepithelial, spindle-shaped cells are inconspicuous
- Mitoses are usually easy to find and increase with recurrent disease
- Necrosis (comedonecrosis) can be detected

ANCILLARY TESTS

Cytology

- Variably arranged, cohesive, solid clusters of basaloid cells
 - Clusters are mixture of ductal cells and rounded, dense, hyaline globular material

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
S100	Positive	Nuclear & cytoplasmic	Nearly all tumor cells but more intensely in spindle cells
Vimentin	Positive	Cytoplasmic	Nearly all tumor cells
CK-PAN	Positive	Cytoplasmic	Accentuates ductal cells but can be seen in all cells
CK7	Positive	Cell membrane	Luminal or duct-like cells
CK19	Positive	Cell membrane	Luminal or duct-like cells
p63	Positive	Nuclear	Variable degree but especially basaloid cells
Actin-sm	Positive	Cytoplasmic	Highlights myoepithelial/basaloid cells
Calponin	Positive	Cytoplasmic	Highlights myoepithelial/basaloid cells
p53	Positive	Nuclear	Increased expression associated with worse clinical outcome
α-fetoprotein	Positive	Cytoplasmic	Rarely detected but seen in tumors with unfavorable outcome
HER2	Positive	Cell membrane	Moderate staining in limited population of cells
Ki-67	Positive	Nuclear	< 2% index: Favorable outcome; 40-80% index: Unfavorable outcome

– Globules are magenta on Diff-Quik

- Background with single myoepithelial and epithelial cells

Histochemistry

- PAS(+) secretion in cystic spaces

Immunohistochemistry

- Tumors show biphasic expression
 - Ductal cells: Cytokeratin, CK7, CK19
 - Basaloid/myoepithelial cells: S100 protein, actin, calponin, p63
- p53 overexpressed in tumors with more aggressive biologic behavior
- AFP may be coexpressed (unfavorable histology cases)
- Increasing Ki-67 labeling associated with unfavorable outcome

DIFFERENTIAL DIAGNOSIS

Pleomorphic Adenoma

- Exceedingly rare in neonatal age group
- Combination of epithelial and myoepithelial cells, with ductal cells **without** invasion
- Chondromyxoid matrix or stroma
- Squamous metaplasia, oncocyctic change

Basal Cell Adenoma

- Very rare in neonatal age group
- Monotonous population of basaloid cells
- Lack mitoses and pleomorphism
- May have excess basal lamina material, hyaline PAS(+) tissue

Adenoid Cystic Carcinoma

- Exceedingly rare in neonatal age group
- Invasive lesion, with strong perineural proclivity
- Cribriform and sieve-like pattern is common
- Peg/carrot-shaped cells, often arranged in palisade
- Reduplicated basement membrane material
- Mucopolysaccharide secretions

Teratoma

- Tumors show elements from all 3 germinative layers

◦ Ectoderm, mesoderm, and endoderm

- Immature tumors
 - Highly malignant
 - Cellular pleomorphism
 - Necrosis
 - Increased mitoses

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Clinical Photograph of Large Parotid Mass

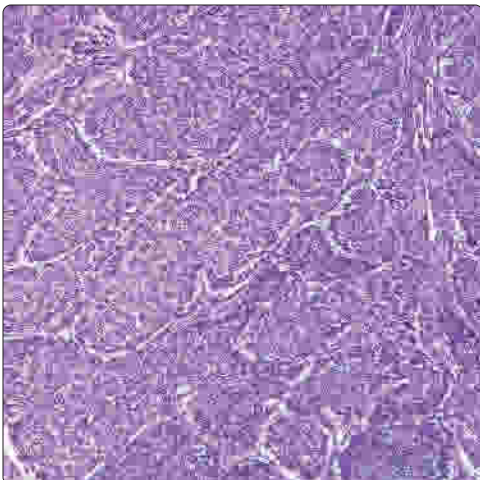


Multinodular Pattern

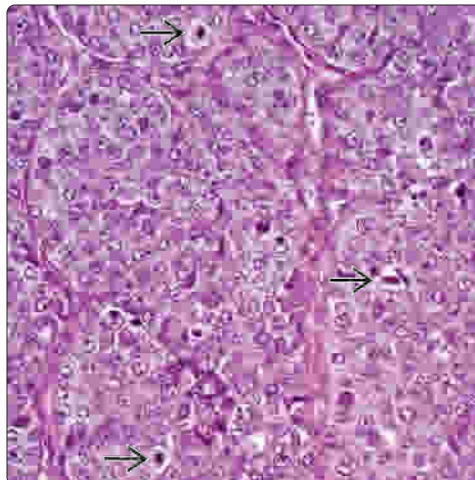



(Left) This boy, less than 1 year old, was noted to have a rapidly enlarging mass in the region of the parotid gland. Note the surface ulceration and involvement of the preauricular, retroauricular, and superior cervical regions. This is a typical presentation of this uncommon neoplasm. **(Right)** There is a multinodular appearance to this tumor showing heavy fibrous connective tissue. There is extension of the tumor into the fibrous connective tissue capsule . (Courtesy R. Foss, DDS.)

Sheets and Lobules of Neoplastic Cells

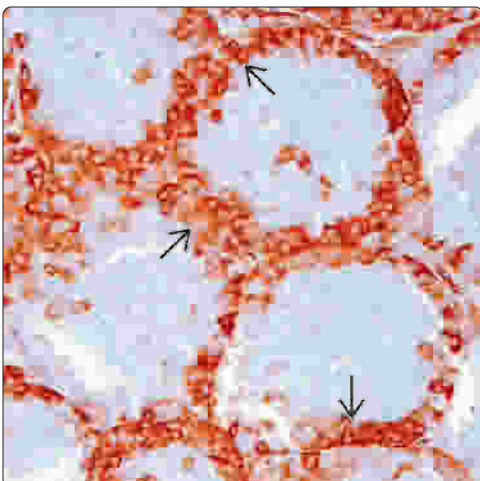


Mitoses Are Easily Identified

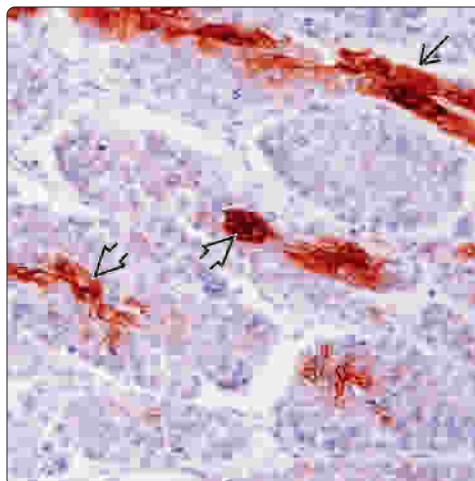





(Left) There are sheets and lobules of cells arranged in a syncytium, with focal palisading at the periphery. The cells are atypical but monotonous. **(Right)** A sheet-like to focally nodular pattern is present in this tumor. Note the vesicular nuclear chromatin distribution and the single prominent nucleoli. Mitotic figures  are easily identified in this tumor.

SMA Highlights Peripheral Cells



CK-PAN Highlights Cuboidal Cells



(Left) Smooth muscle actin shows a very strong decoration of the peripheral cells  in each of the lobules of this sialoblastoma. Other markers (S100 protein, calponin, p63) may also be used to highlight the myoepithelial cells. (Courtesy R. Foss, DDS.) **(Right)** The ductal  and luminal  cells are highlighted with a pan cytokeratin immunohistochemistry. Focal reactivity is noted in the other cells, but the biphasic appearance is accentuated with this stain. (Courtesy R. Foss, DDS.)

Mucoepidermoid Carcinoma

KEY FACTS

TERMINOLOGY

- Malignant epithelial tumor with variable components of mucous, epidermoid, and intermediate cells

CLINICAL ISSUES

- Most common malignant salivary gland tumor
- Wide age range; female > male
- Major glands most commonly affected, followed by minor salivary glands
- Low-grade tumors rarely metastasize
 - t(11;19)(q21;p13): *CRTC1-MAML2* fusion-positive cases have better prognosis
- Positive surgical margins are predictive of recurrence or residual tumor

MACROSCOPIC

- Circumscribed, partially or poorly defined periphery

MICROSCOPIC

- Variably sized cystic spaces

- Contains intermediate cells, epidermoid cells, and mucocytes
 - Mucocytes are arranged in nests or scattered
- Clear cells may be predominant
- Tumor-associated lymphoid proliferation
- Tumor grading very helpful in predicting outcome and management



ANCILLARY TESTS

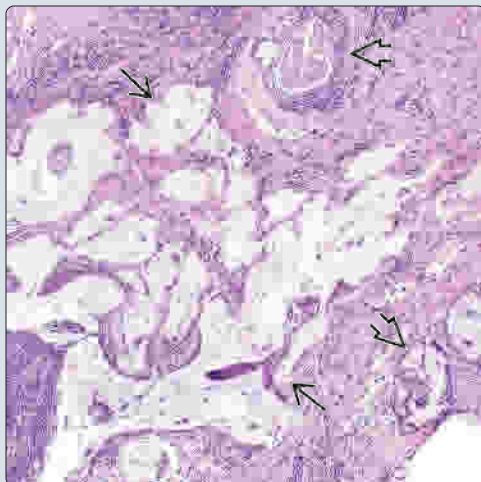
- Mucicarmine-**positive** mucocytes
- *CRTC1-MAML2* fusion is unique

TOP DIFFERENTIAL DIAGNOSES

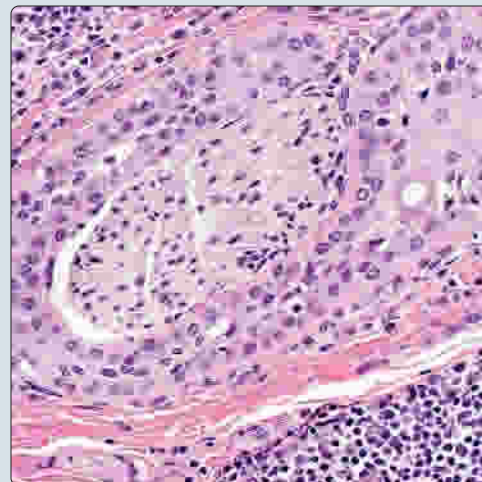
- Sialometaplasia, mucous extravasation reaction
- Cystadenoma, cystadenocarcinoma
- Squamous cell carcinoma, salivary duct carcinoma
- Clear cell carcinoma, epithelial-myoepithelial carcinoma, clear cell malignancies

MEC With Mucinous Extravasation


(Left) There is significant mucus extravasation  in this mucoepidermoid carcinoma (MEC). In addition, the epithelial and mucocyte components are easily identified . (Right) The nerve is noted in the center of the image, completely surrounded by the neoplastic transitional-type epithelium in this MEC. Perineural invasion is one of the features used in tumor grade.

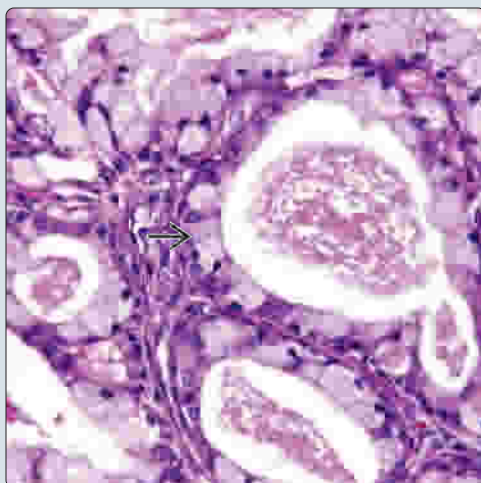


Perineural Invasion

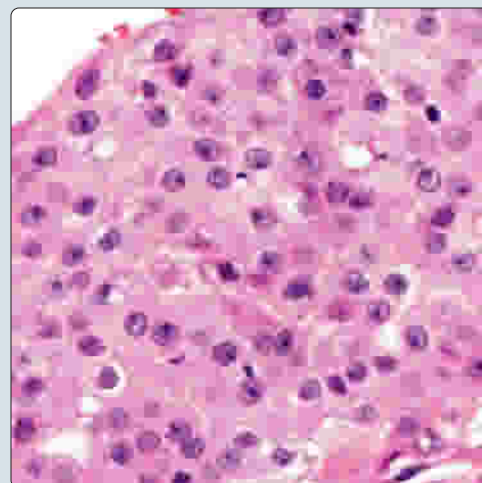


Glands Lined by Mucocytes

(Left) Hematoxylin & eosin stain shows small cystic spaces lined by mucous cells . These cells are large, ovoid, and have abundant foamy cytoplasm. The nuclei are frequently "squashed" toward the periphery. (Right) This epidermoid component of the tumor shows a very bland appearance and well-formed cell borders with a hint of intercellular bridge formation.



Transitional-Type Epithelium



TERMINOLOGY

Abbreviations

- Mucoepidermoid carcinoma (MEC)

Definitions

- Malignant epithelial tumor with variable components of mucous, epidermoid, and intermediate cells

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Ionizing radiation
 - Latent period between irradiation to malignancy varies
 - Long-term follow-up is required

Pathogenesis of Primary Intraosseous Tumors

- Malignant transformation of epithelial lining of odontogenic cysts
 - Favored mechanism
- Malignant transformation of ectopic salivary gland tissue

CLINICAL ISSUES

Epidemiology

- Incidence
 - Salivary gland carcinomas are rare, comprising ~ 0.3% of all cancers
 - Most common malignant salivary gland tumor
 - Represents ~ 16% of all salivary gland tumors
 - Most common salivary gland tumor to arise in gnathic bones
- Age
 - Wide range
 - Most common malignant salivary gland tumor in children
- Sex
 - Female > male

Site

- Major glands
 - Parotid gland is most common location
- Minor glands
 - Palate or buccal mucosa
- Central (primary intraosseous)
 - Originates within jaws
 - Predilection for mandible

Presentation

- Painless, slow-growing mass
- Parotid gland
 - Usually asymptomatic solitary mass
 - Symptomatic
 - Pain, facial numbness and paralysis
 - Drainage from ipsilateral ear
 - Dysphagia, trismus
 - Rapid increase in size
- Minor glands
 - May be misdiagnosed clinically as reactive or inflammatory lesion
 - Swelling, fluctuant, red-blue mass
 - Secondary ulceration occasionally
 - Bleeding or drainage

- Dysphagia, paresthesia
- Primary intraosseous
 - Radiolucent lesion on dental radiograph
 - Swelling, pain, facial asymmetry, trismus
- Rarely associated with other benign salivary gland tumors
 - Can be metachronous or synchronous
 - Pleomorphic adenoma, Warthin tumor, oncocytoma

Treatment

- Surgical approaches
 - Major glands
 - Conservative excision for stage I and II parotid gland tumors
 - Preservation of facial nerve, if possible
 - Complete resection of submandibular gland
 - Neck dissection for metastatic disease, large tumors, or high-grade tumors
 - Minor glands
 - Excision with wide margin
 - Lesion infiltrating or closely abutting bone may require resection of bone
 - Neck dissection for metastatic disease, large tumors, or high-grade tumors
 - Primary intraosseous
 - Enucleation or curettage
 - Segmental resection
 - Neck dissection based on clinical findings
- Adjuvant therapy
 - Radiotherapy
 - Used when inoperable; positive margins
 - High-stage disease
 - Chemotherapy
 - May be useful for high-grade tumors

Prognosis

- Grade is one of most important factors, followed by stage
- Low-grade tumors
 - Rarely metastasize, with 98% disease-specific survival (DSS): 5 years
- High-grade tumors
 - 55-80% metastasize; 65% DSS: 5 years
 - Tend to show increased gene copy number of either *HER2* or *EGFR* in mutually exclusive manner
- Positive surgical margins are predictive of recurrence
- Negative prognostic factors include
 - High grade: Mitoses ($\geq 4/10$ HPF) and necrosis most significant (higher weighting in grade determination)
 - Pleomorphism, focal keratinization, desmoplasia, and lymph node metastasis: Associated with lower DSS
 - Increasing patient age, tumor size, and extraparenchymal extension are less significant
- Lymph node metastases are
 - More common in males than females
 - More common in submandibular gland lesions
 - Developed more frequently in high-grade tumors than low and intermediate grade
- Metastases
 - Predictive of poor prognosis
 - Lung, bone, brain
- Sites of aggressive tumors regardless of grade

Mucoepidermoid Carcinoma

- Submandibular gland has prognosis similar to high-grade lesion
- Tongue and floor of mouth
- t(11;19)(q21;p13): *CRTC1-MAML2* fusion-positive cases have better prognosis
- Primary intraosseous rarely metastasize

IMAGING

General Features

- MR, CT, and radiographs used for major glands
- Minor gland tumors may show erosion of adjacent bone
- Primary intraosseous tumors are generally well-circumscribed radiolucencies

MACROSCOPIC

General Features

- Circumscribed, partially encapsulated, poorly defined
- Cut surface often cystic, sometimes with blood
 - Pink, tan, or yellow

Size

- Highly variable
 - < 1 cm to large disfiguring masses

MICROSCOPIC

Histologic Features

- Cystic spaces
 - Often filled with mucin
 - Occasionally papillary projections are present
- Epidermoid cells
 - Nests or scattered polygonal cells
- Intermediate cells
 - Often found in nests or sheets
 - Large polygonal epidermoid cells and small basal cells
- Mucous cells
 - In groups or individually scattered
 - Intracytoplasmic mucin within cleared or vacuolated cells
- Clear cells
 - Usually < 10% of cells but can be dominant finding
 - May contain glycogen or mucin
- Spilled mucus incites inflammatory response
 - May be misinterpreted as mucous escape reaction
- Tumor-associated lymphoid proliferation (TALP)
 - Lymphoid cells with occasional germinal centers
 - May be confused with metastatic disease to lymph node
- Necrosis, anaplasia, and mitoses variably present
- Perineural and lymph vascular invasion
- **Sarcomatoid** transformation may rarely be seen
- **Sclerosing mucoepidermoid carcinoma**
 - Fibrous stroma is plentiful and can be hyalinized
 - Inflammatory cells (including eosinophils) are seen

ANCILLARY TESTS

Cytology

- Clusters of bland intermediate or epithelial cells
- Mucocytes within clusters
- Variable amounts of mucin in background
- May be hypocellular or acellular if cystic areas are sampled

- Papanicolaou stain: Epithelial cells with dense, green-blue cytoplasm
- Diff-Quik: Mucocytes with intracellular, red-granular mucin droplet
 - Epithelial cells with light pink-purple cytoplasm

Frozen Sections

- Usually quite distinctive
- High-grade lesions may be misdiagnosed as squamous cell carcinoma

Immunohistochemistry

- p63
 - Strong, basal cell nuclear reaction
 - May highlight intermediate as well as epidermoid cells
 - Highly reactive lesions may indicate poor prognosis
- CK5/6
 - Highlights epidermoid-type cells but is often **negative** in transitional cells
- Ki-67
 - High expression seen with increased proliferation, usually indicative of high-grade tumor
 - Overexpression may serve as indicator of poor prognosis
- HER2
 - Tends to be strongly reactive in high-grade tumors
 - Overexpression may serve as indication for poor prognosis
 - Reactivity may guide future therapy with Herceptin
 - All 7 high-grade MECs had increased gene copy number of either *HER2* or *EGFR*, in mutually exclusive manner
- p16
 - **Positive** in up to 60% of tumors (higher in glandular than squamoid areas)
 - **No** match to transcriptionally active HPV

Genetic Testing

- t(11;19)(q21;p13) seen in 55-65% of MEC
 - This translocation fuses CREB-regulated transcription coactivator 1 (*CRTC1*, formerly *MECT1*) (exon 1 of gene at 19p13) with Mastermind-like gene family (*MAML2*) (exons 2–5 of gene at 11q21)
 - Identified in low- to intermediate-grade tumors usually
 - Tumors with few copy number alterations (usually *CRTC1-MAML2*) seem to have better prognosis
- t(11;15)(q21;q26) translocation results in *CRTC3/MAML2* gene fusion (~ 5% of tumors), usually seen in younger patients
- t(6;22)(p21;q12) translocation with *EWSR1-POU5F1* gene fusion, seen in high-grade tumors
- *CDKN2A* deletions seen in more aggressive *MAML2* fusion-positive tumors
- Aneuploid tumors
 - Higher recurrence rate and decreased survival
 - Increased cervical lymph node involvement

DIFFERENTIAL DIAGNOSIS

Sialometaplasia

- Usually in lobular pattern, lacking cystic growth, no intermediate cells
- Mucocytes are residual to salivary gland

Mucous Extravasation Reaction

- Lacks intermediate cells and epithelial cells
- Mucus found primarily in macrophages

Squamous Cell Carcinoma (Often Metastatic)

- Known skin or mucosal primary site
- Usually has well-developed keratinization and intercellular bridges
- Lacks intermediate cells and mucocytes

Salivary Duct Carcinoma

- High-grade tumor, often with Roman bridge pattern, comedonecrosis, significant pleomorphism, high mitotic rate
- **Positive:** Androgen receptor; **negative:** CK5/6, p63

Clear Cell Malignancies

- Clear cell adenocarcinoma
 - Lacks intermediate cells or mucocyte differentiation
- Epithelial-myoepithelial carcinoma
 - Lacks intermediate cells, mucocyte differentiation
 - Shows distinct and characteristic biphasic glandular proliferation

Cystadenoma

- Not infiltrative
- Lacks sheets of epithelial proliferations and intermediate cells
- Focal rare mucocytes

Cystadenocarcinoma

- Lacks intermediate cells
- Focal rare mucocytes

DDx of Primary Intraosseous Tumors

- Glandular odontogenic tumor
- Reactive cyst with mucous metaplasia
- Clear cell odontogenic carcinoma

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Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CK-PAN	Positive	Cytoplasmic	Most cells, although only focally for mucocytes
CK5/6	Positive	Cytoplasmic	More common in epidermoid than transitional cells
CK7	Positive	Cytoplasmic	More intense staining for intermediate/transitional cells
p63	Positive	Nuclear	Basal cell reaction; strong staining suggests worse prognosis
CK14	Positive	Cytoplasmic	
CK19	Positive	Cytoplasmic	
CK17	Positive	Cytoplasmic	
EpCam/BER-EP4/CD326	Positive	Cell membrane & cytoplasm	
HER2	Positive	Cell membrane	Greater degree of positivity, suggests higher grade tumor
Ki-67	Positive	Nuclear	Higher proliferation index, higher grade of tumor and worse prognosis
Actin-HHF-35	Equivocal	Cytoplasmic	5% positivity
p16	Positive	Nuclear & cytoplasmic	Highlights subpopulation of neoplastic cells
CK20	Negative	Cytoplasmic	
S100	Negative	Nuclear & cytoplasmic	
GFAP	Negative	Cytoplasmic	
Mammaglobin	Negative		Rarely may be seen
Androgen receptor	Negative		
GCDFP-15	Negative		

Tumor Grading

Parameter	Point Value
Intracystic component > 20%	2
Neural invasion present	2
Necrosis present	3
4 or more mitoses per 10 HPF	3
Anaplasia	4
Grade	Total point score
Low grade	0-4
Intermediate grade	5-6
High grade	7 or more

Adapted from Auclair PL et al: Mucoepidermoid carcinoma of intraoral salivary glands: evaluation and application of grading criteria in 143 cases. Cancer. 69(8):1217-24, 1998.

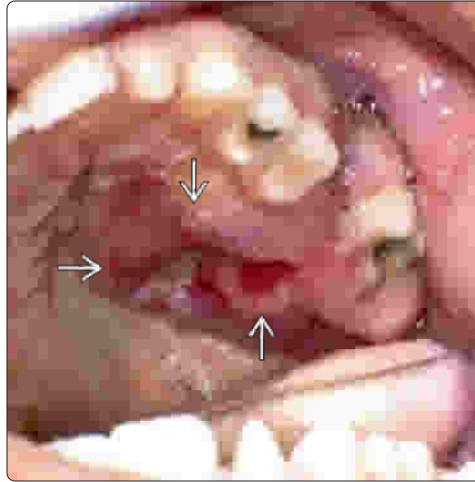
Histochemical Studies

Histochemical Stain	Reactivity	Staining Pattern	Comment
Mucicarmine	Positive	Cytoplasmic	Identifies mucocytes
Periodic acid-Schiff (PAS)	Positive	Cytoplasmic	Identifies glycogen
Alcian blue	Positive	Cytoplasmic	Identifies mucocytes
PAS-D	Negative		

Angle of Jaw Mass



Hard Palate MEC Clinical Photo



(Left) A multinodular, cystic mass is present in the left parotid gland of this elderly man. The patient had experienced symptoms for several years, but only recently had the mass become more erythematous. MEC may have a long clinical history before presentation. (Right) Clinical photograph shows an ulcerated red mass of the posterior lateral hard palate. Microscopic review confirmed a low-grade MEC arising from a minor salivary gland. Palate primaries usually do not have a capsule.

CT of Large Parotid Gland Tumor

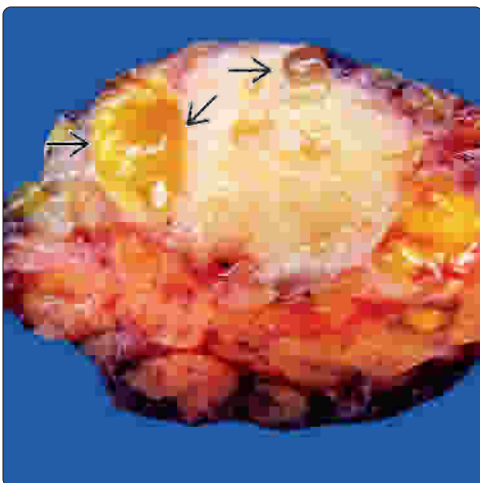


T2WI MR of Parotid Gland Cystic Tumor



(Left) Axial contrast-enhanced CT shows an invasive high-grade mucoepidermoid carcinoma involving the superficial and deep lobes. There is significant destruction of the parotid parenchyma by the tumor. Notice the single intraparotid lymph node. (Right) Corresponding coronal T2-weighted MR shows a well-defined, high signal tumor with cystic necrosis. This could be easily mistaken for another tumor type.

Cystic Parotid Gland Tumor



Unilocular Cystic Parotid Mass



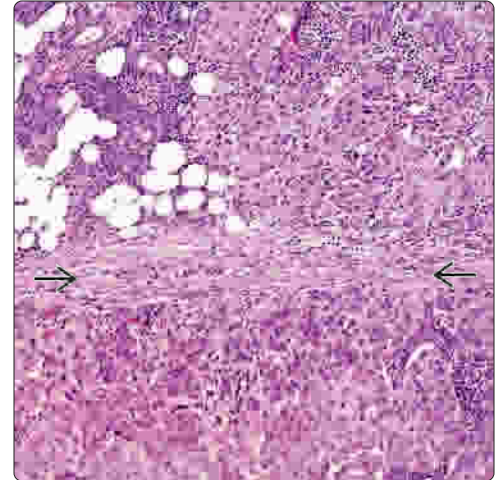
(Left) Gross photograph shows a tumor with a tan-yellow cut surface. Mucoïd material can be seen in the cystic spaces. The remaining parenchyma is compressed toward the periphery. (Right) Gross photograph shows a predominantly unicystic mucoepidermoid carcinoma. The lumen was filled with thick, tenacious, mucoïd material. This type of lesion can easily mimic a mucocele, clinically and macroscopically.

(Left) H&E stain shows a cystic tumor with areas of spilled mucus [X]. Based on the greater than 20% cystic component, this pattern suggests a low-grade tumor (assuming a total score of 4 or less). **(Right)** The neoplastic cells are noted beyond the capsule [X], expanding into the adjacent parenchyma. It is important to remember that salivary gland parenchyma has fat; do not interpret as extraglandular extension.

Multicystic Mass

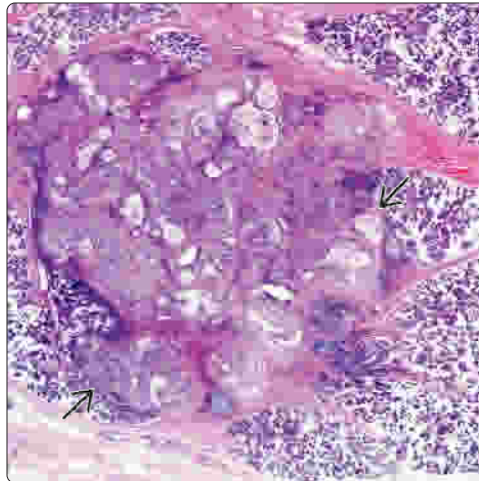


Parenchymal Extension

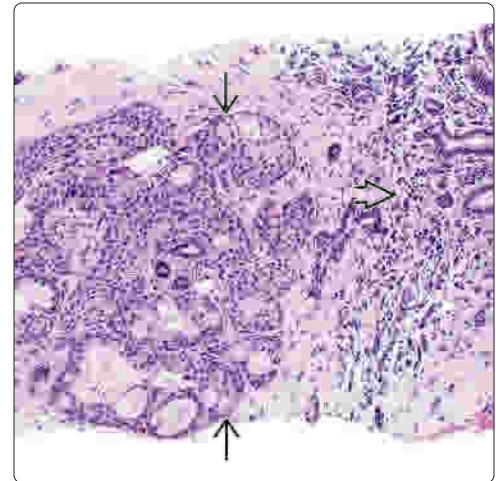


(Left) A low-power view shows the infiltrative periphery, with several areas of the tumor in direct contact with the parenchyma [X]. There are several cysts easily identified throughout. **(Right)** In core needle biopsies, especially those mucosal-based, minor salivary gland lesions are fraught with difficulty. There is a neoplasm with epidermoid and mucocytes [X] separated from the minor salivary gland tissue [X].

Unencapsulated Neoplasm With Invasion

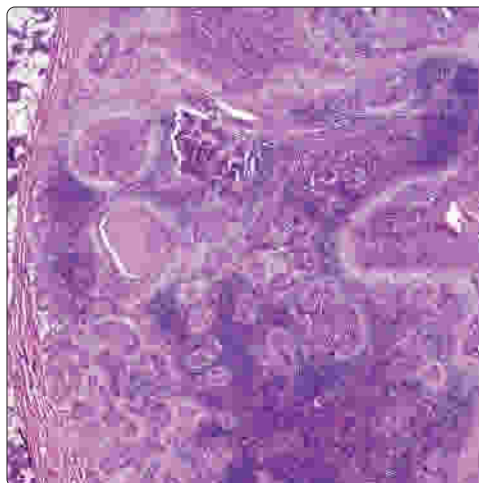


Core Needle Biopsy of MEC

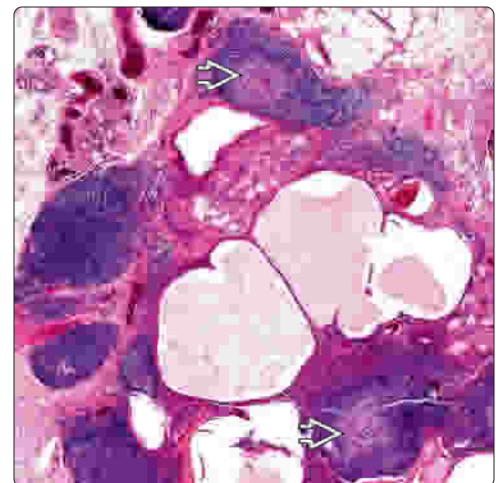


(Left) This MEC shows infiltration into the adjacent parenchyma. This is associated with a very well-developed tumor-associated lymphoid proliferation (TALP). **(Right)** This MEC has TALP. Well-formed germinal centers are easily identified [X], but no capsule is seen, indicating that this is not metastatic disease in a lymph node.

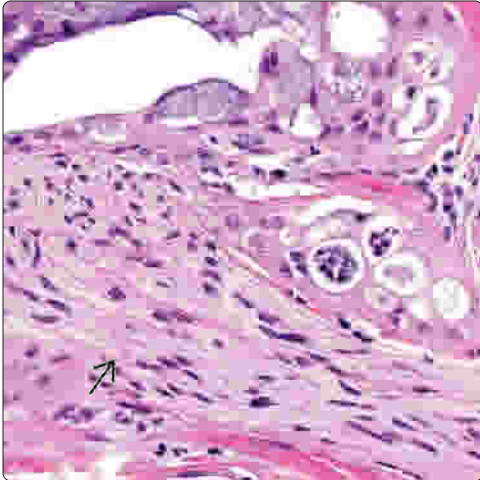
Tumor-Associated Lymphoid Proliferation



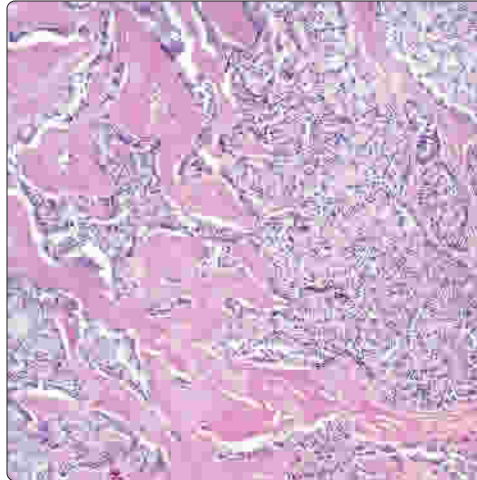
Cystic Tumor With TALP



Perineural Invasion by MEC

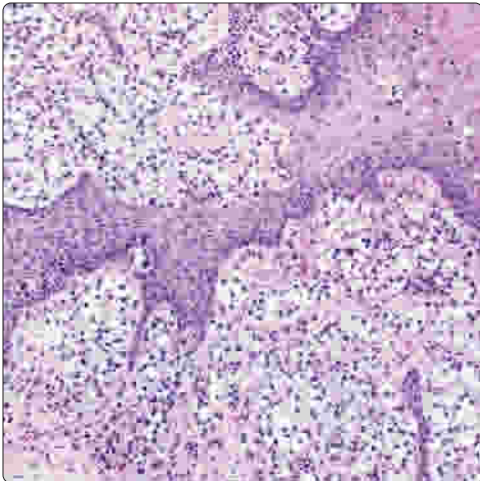


Tumor Hyalinization

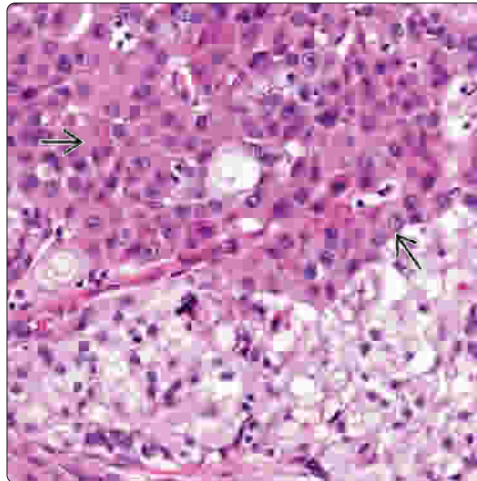


(Left) The presence of perineural invasion nearly always increases the grade of the tumor. Here the tumor is immediately adjacent to nerve tissue [2], showing epidermoid cells and mucocytes. (Right) Although not commonly present, heavy intratumoral sclerosis or fibrosis can be seen in MEC.

Clear Cell Change in MEC

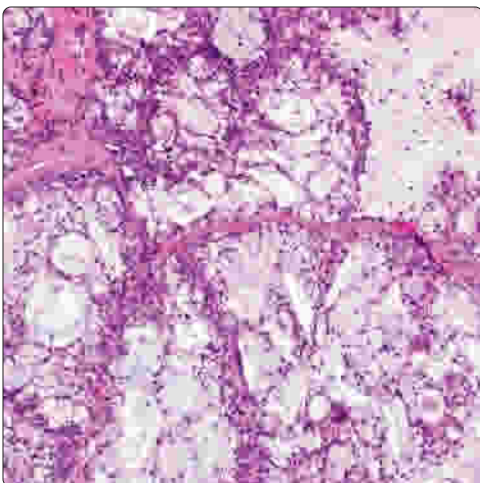


Epidermoid and Intermediate Cells

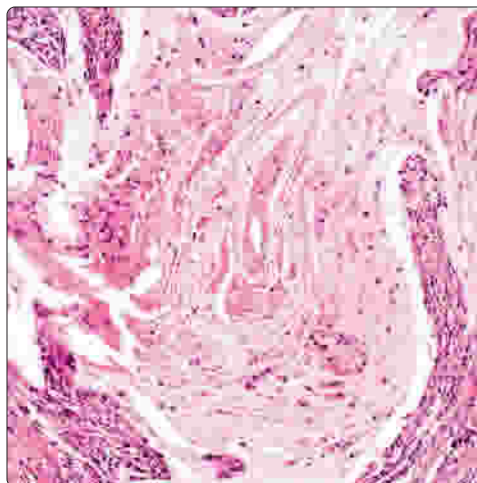


(Left) The surface epithelium is intimately associated with a clear cell tumor that in other areas showed the characteristic features of MEC. Sampling is important, but performing a mucicarmine stain to highlight the mucin is also helpful. (Right) The epidermoid component [2] shows a very hard, eosinophilic cytoplasm surrounding a slightly vesicular nuclei. The lower half shows the more intermediate cells. Clear cell change is also present, and should not be equated with mucin production.

Low-Grade MEC




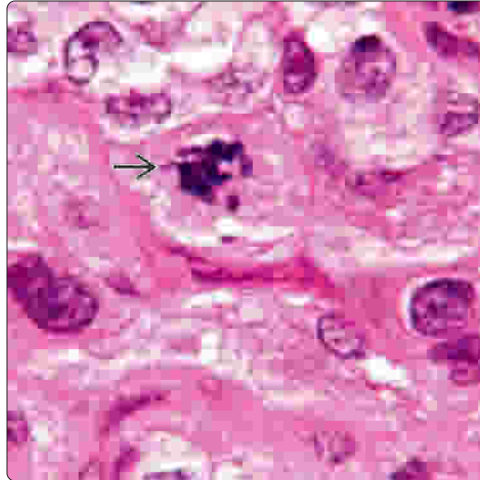
Pools of Mucin and Histiocytes



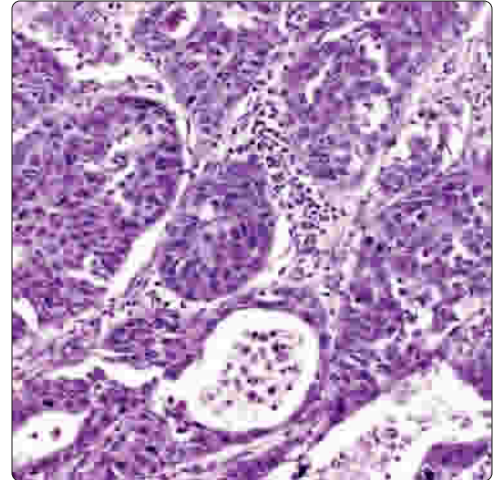
(Left) This is the characteristic appearance of a MEC, showing intermediate cells, epidermoid cells, and mucocytes with cyst formation and mucinous debris. (Right) Hematoxylin & eosin stain shows a pool of free mucus that has caused an inflammatory response. The mucinous material may contain inflammatory debris and histiocytes. These should not be mistaken for true mucocytes, which should be sought in the lining epithelium.

Atypical Mitosis

(Left) Hematoxylin & eosin stain shows a high-power view of an atypical mitotic figure  within a pleomorphic high-grade tumor. There is a transitional epithelial proliferation immediately adjacent to this atypical mitotic figure. (Right) Nuclear pleomorphism and a solid pattern of growth is seen in this tumor. Mitoses are increased, and intracystic debris and inflammation is noted.

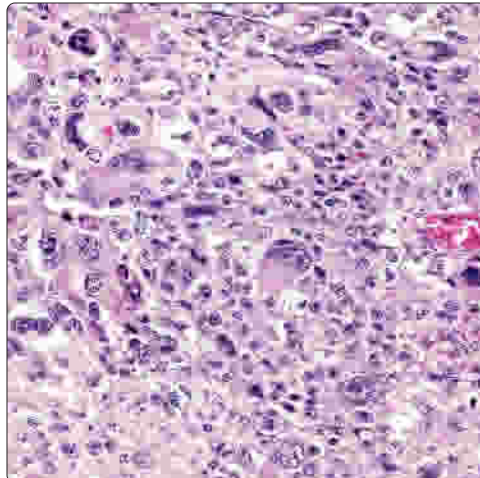


Solid Pattern With Moderate Pleomorphism

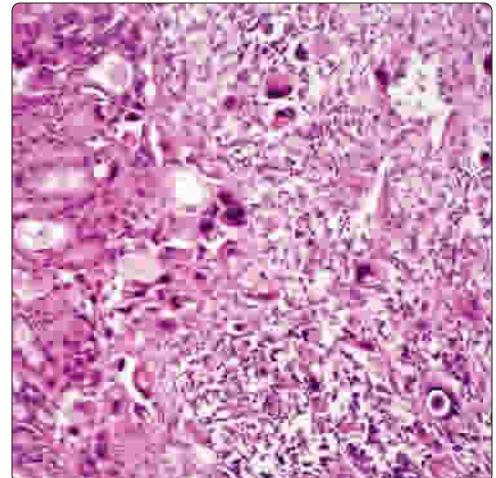


Profound Nuclear Pleomorphism



(Left) The designation of profound pleomorphism is often difficult to qualify or quantify. However, this field shows a very high-grade MEC in which there was profound nuclear pleomorphism. This feature is given a 4 score in the grading schemes. (Right) It is not uncommon to have a MEC undergo spindle cell transformation to a more sarcomatoid or undifferentiated appearance. This undifferentiated tumor portends a poor prognosis.

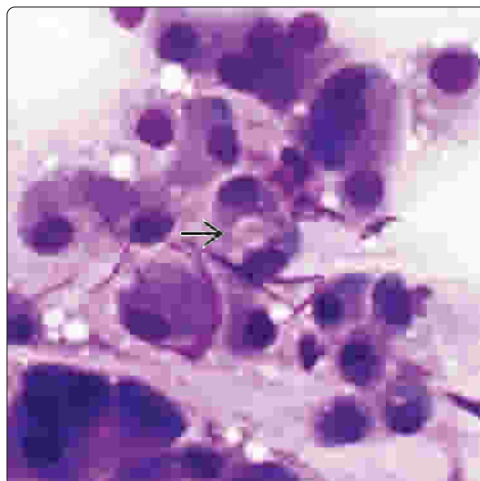


High-Grade Transformation

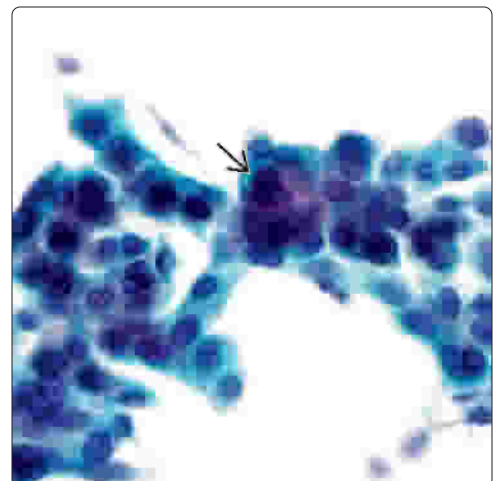


Intracellular Mucin Vacuole

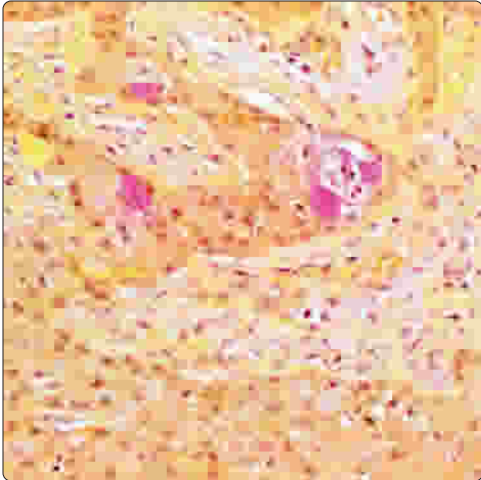
(Left) There is a well-formed mucocyte  in the center of the field seen here. It is surrounded by epidermoid or transitional cells. Note the bluish appearance to the cytoplasm, which is similar to squamous cells. (Right) This cytology smear demonstrates sheets and clusters of epidermoid-transitional cells with opaque cytoplasm. There is a suggestion of a vacuole within the cytoplasm  of 1 of the neoplastic cells.



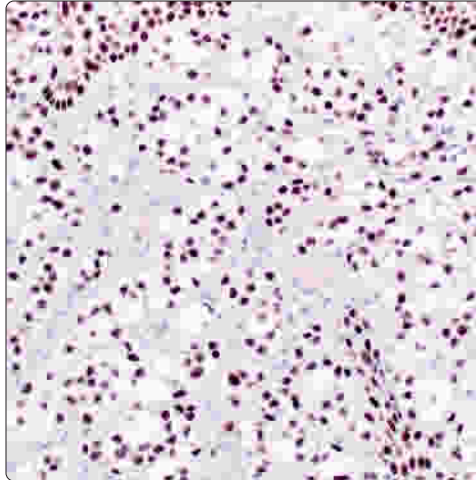
Epidermoid Cells in Sheets



Strong Intracytoplasmic Mucin

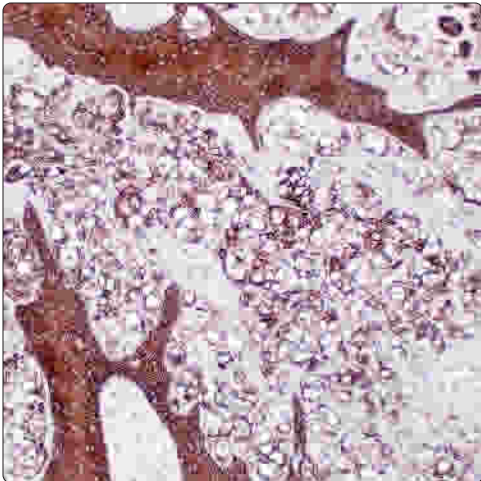


Strong p63 Nuclear Reaction

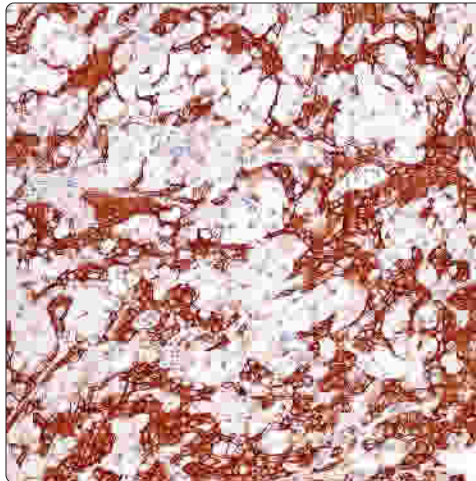


(Left) A mucicarmine stain can be used to highlight intracytoplasmic mucin droplets, while it also highlights extracellular mucinous material. **(Right)** Several immunohistochemistry studies can be positive in MEC, with p63 highlighting many of the neoplastic cells in this clear cell variant.

Strong CK5/6 Reaction

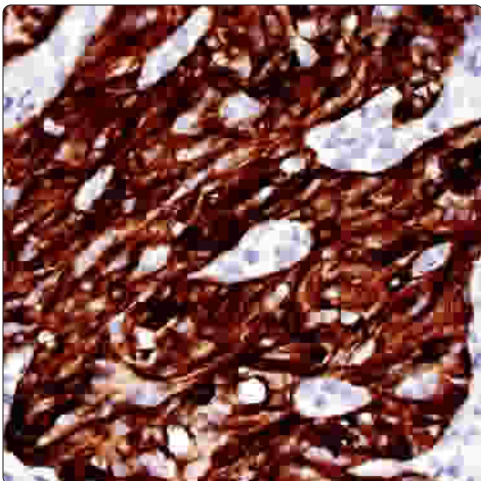


Strong CK5/6 in Intermediate Cells

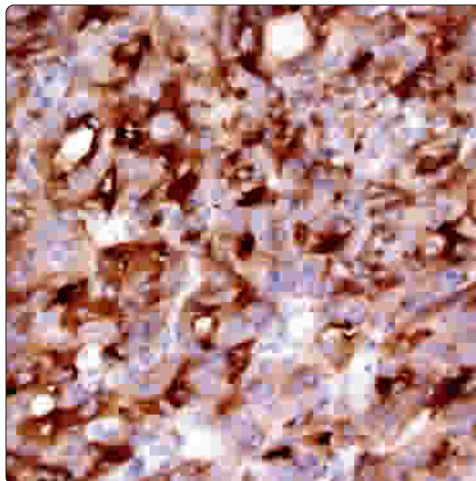


(Left) The surface squamous mucosa serves as an internal control for the strong and diffuse CK5/6 immunoreactivity seen in this MEC. **(Right)** The CK5/6 in this case highlights the intermediate cells, but the mucocytes are negative. There is abundant clear cytoplasm in many of these cells.

Strong CK7 Immunoreactivity



EMA Accentuates Mucocytes



(Left) CK7 strongly and diffusely highlights all of the neoplastic cells, not really creating any specific separation between the various intermediate, epidermoid, or mucus-type cells. **(Right)** Epithelial membrane antigens yield a strong and diffuse cytoplasmic reaction, giving a darker intensity in the mucinous areas.

KEY FACTS

TERMINOLOGY

- Malignant epithelial tumor with myoepithelial and ductal differentiation

CLINICAL ISSUES

- 4th most common malignant salivary gland tumor
- Found with nearly equal frequency in major and minor salivary glands
- Adults primarily, with peak in 6th decade
- Presentation
 - Mass
 - Tenderness or pain
 - Facial nerve paralysis
- Tumors commonly recur and may develop late-onset metastases
- Treated with radical excision

MICROSCOPIC

- Present with variety of patterns

- Cribriform, tubular, solid, or combination
- Cells are usually small, with limited eosinophilic to clear cytoplasm
- Nuclei are oval to sharply angulated (peg-shaped), with coarse chromatin and small nucleoli
- Mitotic figures are rare

ANCILLARY TESTS

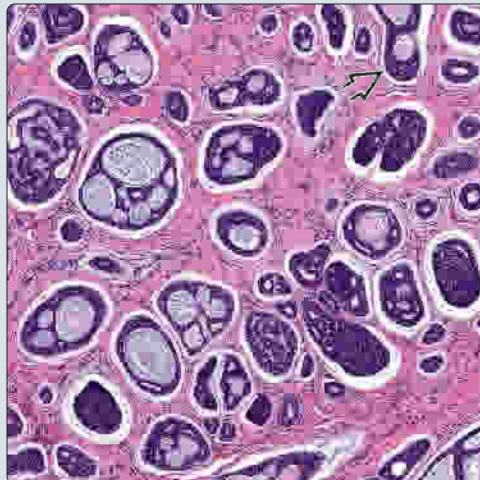
- Multiple nerve sections may be submitted for frozen section
 - Tumor may "skip"
- *MYB* may help confirm diagnosis in difficult cases

TOP DIFFERENTIAL DIAGNOSES

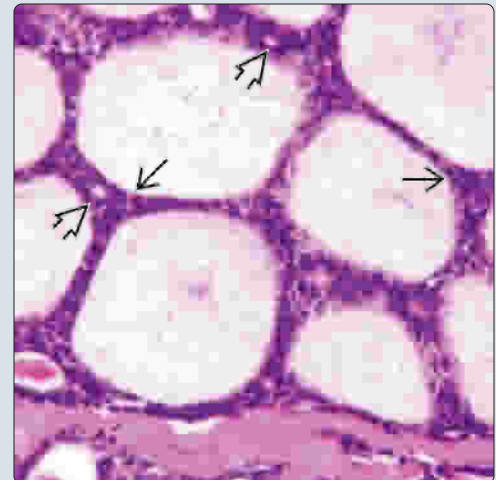
- Polymorphous low-grade adenocarcinoma, pleomorphic adenoma, basal cell adenoma, basal cell adenocarcinoma, epithelial-myoepithelial carcinoma
- Basaloid squamous cell carcinoma, skin cylindroma, sialoblastoma, neuroendocrine carcinoma

Classic Cribriform Pattern

(Left) This tumor shows a cribriform pattern. Despite the appearance, the cyst-like spaces are actually connected to the surrounding stroma. The tumor cells are often described as creating C-shapes that partially encircle the stroma. (Right) This tumor is arranged in a cribriform pattern, the most common, often described as looking like "Swiss cheese" or an old fashion "telephone dial." Note the dark angulated cells and the small ducts.



Characteristic "Swiss Cheese" Growth

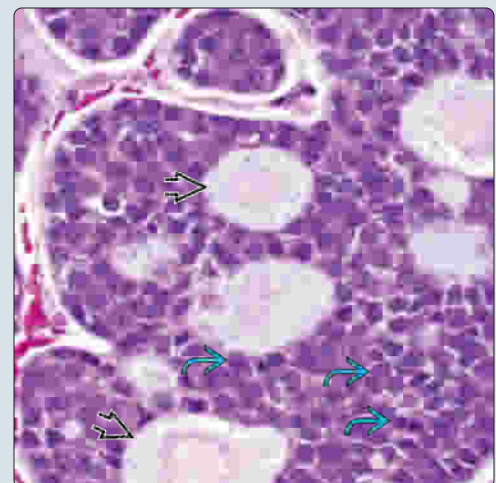


Hyalinized Basement Membrane

(Left) Hematoxylin and eosin image shows the very dense, brightly eosinophilic, hyalinized stroma seen in adenoid cystic carcinoma (ACC). This same reduplicated basement membrane material may be seen in cytology, helpful in making a diagnosis. (Right) This medium-power image shows angular cells mixed with oval cells. The presence of angular cells, even mixed with oval cells, points toward ACC rather than PLGA, which is generally described as having uniformly bland oval to polygonal cells. Note the pseudocystic spaces.



Angular Nuclei and Cells



TERMINOLOGY

Abbreviations

- Adenoid cystic carcinoma (ACC or ACCa)

Synonyms

- Adenocystic carcinoma
 - Outdated terminology
 - May be confused with carcinoma of eccrine origin

Definitions

- Malignant epithelial tumor with myoepithelial and ductal differentiation

CLINICAL ISSUES

Epidemiology

- Incidence
 - 4th most common malignant salivary gland tumor
- Age
 - Adults, peak in 6th decade
 - Rare in children
- Sex
 - Male < female (2:3)

Site

- Found with essentially equal frequency in major and minor salivary glands
- Major
 - Parotid gland > > submandibular > sublingual
- Minor
 - Palate most frequently affected
 - Tongue > lip
- Other
 - Sinonasal, nasopharynx, larynx, trachea, and lacrimal gland
 - Other sites in body: Breast and lung

Presentation

- Mass is most common presenting symptom
- Tenderness or pain with facial nerve paralysis
- Swelling
- Intraoral lesions may be ulcerated

Treatment

- Options, risks, complications
 - Extensive resections may result in significant cosmetic issues
- Surgical approaches
 - Radical excision
 - Reconstruction when indicated
- Adjuvant therapy
 - Chemotherapy is occasionally used for large tumors or late-stage tumors
 - No definitive protocols
- Radiation
 - Conflicting reports on effectiveness

Prognosis

- Clinical stage predicts outcome and survival
- High incidence of recurrence
- Characterized by late-onset metastases

- 5-yr survival rate is good; 20-yr survival rate is poor
- Patients with solid pattern tumors have worse prognosis
- Poor prognostic factors
 - Large tumors, > 4 cm
 - Regional lymph node metastasis (uncommon)
 - Distant metastasis: Lung and bone
 - Perineural invasion
 - Presence of solid component
 - High reactivity with Ki-67
 - High MYB expression (worse patient survival)
- Surgical margin status does not seem to affect survival
- Anatomic site affects outcome
 - Palatal lesions have best outcome
 - Parotid gland tumors have better prognosis than submandibular gland tumors

IMAGING

Radiographic Findings

- Bone destruction may be present

MACROSCOPIC

General Features

- Poorly circumscribed and unencapsulated
 - Rarely encapsulated
- Firm, white-gray cut surface

Size

- Quite variable, although can be large

MICROSCOPIC

Histologic Features

- Infiltrative
 - Perineural invasion is commonly seen
 - Infiltrates into fat, skeletal muscle, soft tissue, destroying residual salivary gland tissue
- Combinations of patterns usually present, although one predominates
- **Cribriform** pattern
 - Looks like "Swiss cheese" or "telephone dial"
 - Epithelial nests contain pseudocysts
 - Pseudocysts are not true glandular lumens but are part of tumor stroma
 - Pseudocysts contain one or both of
 - Amorphous glycosaminoglycans
 - Hyalinized basal lamina
- **Tubular** pattern
 - Lumina are more conspicuous
 - True lumina surrounded by ductal cells with myoepithelial cells forming 2nd layer
 - Small nests separated by eosinophilic hyalinized stroma
- **Solid** pattern
 - Minimum of 30% solid growth required
 - Greater degree of nuclear pleomorphism than in other types
 - Associated with increased mitotic activity
 - Necrosis may be present
- **Cytologic** features
 - Small to medium cells with eosinophilic to clear cytoplasm

- Nuclei are oval to sharply angulated with coarse, basophilic chromatin
 - Occasional small nucleoli
- Mitotic figures are rare
 - Except for solid pattern

ANCILLARY TESTS

Cytology

- May be difficult to distinguish from other tumors
- Cohesive cellular clusters surrounding "balls" of mucopolysaccharide material
- Peg- or carrot-shaped nuclei
- High nuclear:cytoplasmic ratio
- Coarse nuclear chromatin
- Characteristic round, scattered fragments of mucopolysaccharide material surrounded by cells
 - **Diff-Quik:** Purple-pink to magenta, bubblegum-like
 - **Papanicolaou:** Light green, orange, or clear
 - Cells are at periphery, not embedded within stroma

Frozen Sections

- Multiple peripheral nerve sections are often submitted: Tumor "skip"

Histochemistry

- Alcian blue: Highlights basement membrane material of pseudolumina
- PAS: Highlights basement membrane material of pseudolumina

Immunohistochemistry

- May have limited practical use
 - Tumors in differential diagnosis often react similarly
 - p63, p40 and *MYB* may show differential expression between tumors in differential diagnosis
- MCM2: Expressed in G1/G2/S and stains cells that are enabled to proliferate
 - Overexpressed in many tumors, but MCM2 has highest expression in ACC (> 10%) and is low to absent in polymorphous low-grade adenocarcinoma (PLGA) and pleomorphic adenoma (< 10%)

Genetic Testing

- Many have t(6;9) chromosomal translocation resulting in *MYB-NFIB* fusion
 - Noncanonical *MYB-NFIB* gene fusions occur in subset of tumors
- *EWSR1-ATF1* gene fusions
- ~ 50% have loss of chromosome 12q12
- Loss of heterozygosity at 6q23-25: Associated with poorer prognosis
- Alteration of p53: Associated with tumor recurrence and progression to solid type

DIFFERENTIAL DIAGNOSIS

Polymorphous Low-Grade Adenocarcinoma

- Most difficult to distinguish from ACC
- Only identified in minor salivary glands
- Low-power pattern shows
 - Single-cell invasion, often in columns or rows

- Targetoid, swirling, or eye-of-storm patterns around nerves
- Bland uniform oval to round cells
 - Lacks pleomorphism and lacks increased mitoses
 - Nuclear chromatin is vesicular to delicate
- Immunohistochemistry may show differential expression
 - MCM2 and Ki-67 much higher in ACC than PLGA
 - CD117(+) in ACC (~ 100%) and in some PLGA (~ 25%)
 - p63(+)/p40(-) in PLGA; p63(+)/p40(+) in ACC

Pleomorphic Adenoma

- Lacks infiltration, especially perineural invasion
- Myxochondroid matrix material is different, with blending of epithelial cells into matrix
- Plasmacytoid and spindled cells common
- Ducts are present
- Squamous and oncocytic metaplasia more common

Basal Cell Adenoma

- Lacks infiltrative growth
- Shows well-developed peripheral palisading
- Lacks pleomorphism and increased mitoses
- β -catenin: Nuclear **positive** in basal cell adenoma; **negative** in basal cell adenocarcinoma

Basal Cell Adenocarcinoma

- Shows well-developed peripheral palisading
- Invasive growth defines this tumor
- Lacks pleomorphism with limited mitoses
- Lacks glycosaminoglycan material but includes basal lamina

Epithelial-Myoepithelial Carcinoma

- Periductal cells are large, not angulated, and clear
- Lacks pleomorphism and increased mitoses

Carcinoma Ex-Pleomorphic Adenoma

- Features of pleomorphic adenoma are present (or there is clinical history)
- ACC may be malignant component of carcinoma ex-pleomorphic adenoma

Basaloid Squamous Cell Carcinoma

- May be associated with overlying epithelial dysplasia
- Usually found in base of tongue or hypopharynx
- Distinctive comedonecrosis
- Squamous differentiation is required; not seen in ACC

Skin Cylindroma

- Skin tumor, common in head and neck
- Epithelial islands arranged in jigsaw pattern surrounded by thickened basement membrane
- Cytologically bland

Sialoblastoma

- Develops almost exclusively in children
- Basaloid cells with vesicular nuclei
- Peripheral palisading of nuclei is common
- Squamous morules are helpful

Neuroendocrine Carcinoma

- Rare tumor, difficult to diagnose on small biopsies
- Lacks cribriform pattern
- **Positive** with neuroendocrine markers

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CK-PAN	Positive	Cytoplasmic	All tumor cells can be differentially expressed
CD117	Positive	Cell membrane & cytoplasm	Solid type more reactive than tubular type
Actin-sm	Positive	Cytoplasmic	Abluminal cells
Calponin	Positive	Cytoplasmic	Abluminal cells
p63	Positive	Nuclear	Abluminal cells
CK7	Positive	Cytoplasmic	All tumor cells
SMHC	Positive	Cytoplasmic	Abluminal cells
S100	Positive	Nuclear & cytoplasmic	Abluminal cells
p40	Positive	Nuclear	
myb	Positive	Nuclear	Most tumors are positive
MCM2	Positive	Nuclear	Usually > 10% of nuclei react
TTF-1	Negative		
CD56	Negative		
GFAP	Equivocal	Cytoplasmic	Limited reactivity in only isolated cells

Grading of Adenoid Cystic Carcinoma

Parameter	Grade 1	Grade 2	Grade 3
Percentage of tumors in each grade	45%	35%	20%
Circumscription	Good	Deceptive or irregular	Never
Necrosis	Absent	May be present	Easily identified
Bone invasion	Absent	May be present	Often present
Perineural invasion (nerves beyond gland raise grade)	Present	Easily identified	Significant, including large nerves
Dominant pattern	Tubular	Cribriform	Solid
Pleomorphism	Limited	Present	Profound variability
Mitoses	Rare	Few	Many
Recurrences	50%	80%	100%
15-yr survival	39%	26%	5%

Survival Rates Based on Stage

Stage	10-Year Survival Rate
I	75%
II	43%
III & IV	15%

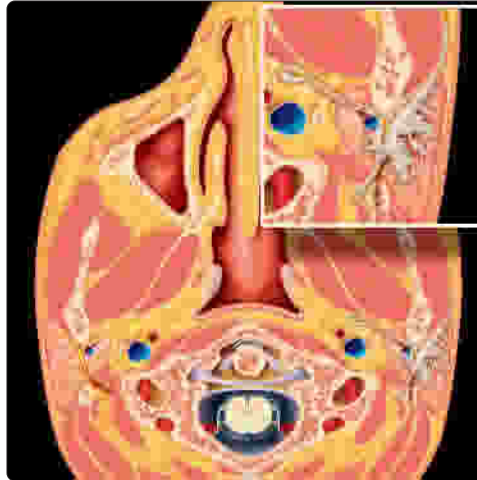
Adapted from Spiro RH et al. Am J Surg. 164(6):623-8, 1992.

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Graphic of Perineural Invasion

(Left) This graphic demonstrates the proclivity of adenoid cystic carcinoma for perineural invasion. This feature is not exclusive to this tumor, but, in ACC, the tumor often "skips" along the nerve, making frozen section margins very challenging and perhaps unreliable. (Right) An axial T1 enhanced fat-saturated MR demonstrates an invasive deep and superficial lobe parotid ACC involving the stylomastoid foramen.

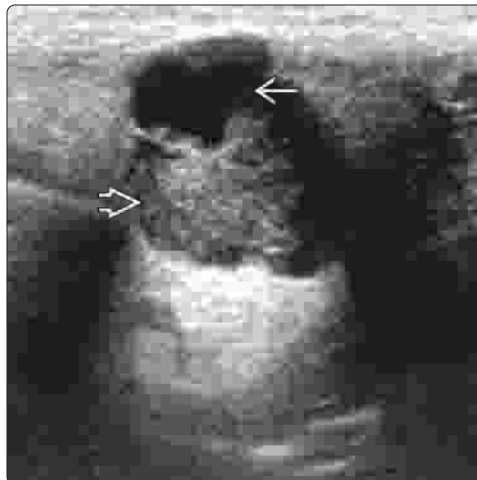


MR: Parotid Gland Neoplasm

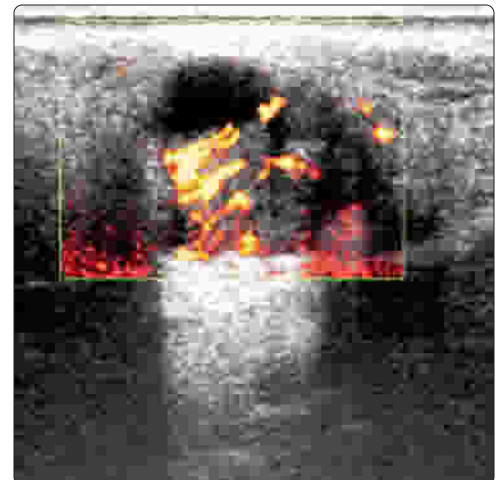


US of Adenoid Cystic Carcinoma

(Left) Longitudinal grayscale US shows an ACC as a hypoechoic, heterogeneous tumor with cystic necrosis. The tumor bulges out of the glandular contour. Still, this tumor is fairly well defined and simulates a pleomorphic adenoma radiographically. (Right) Power Doppler US shows prominent vessels in the solid portion of the tumor. This increased flow is not unique to ACC, but it does raise the possibility of a malignancy vs. a benign tumor.

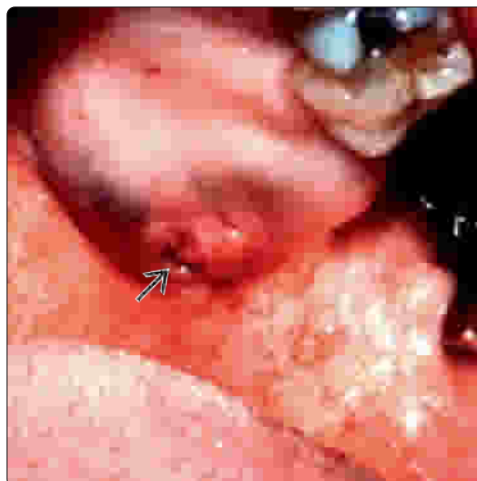


Doppler US With Chaotic Blood Flow

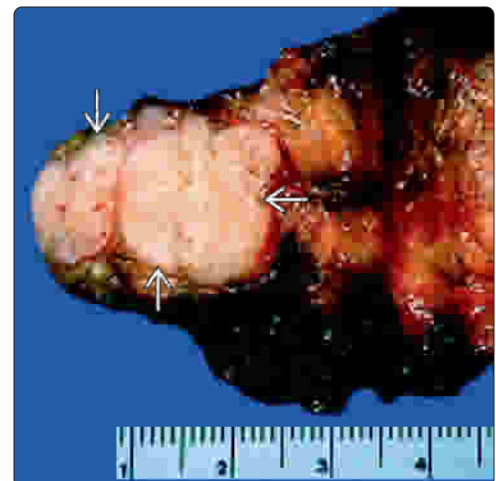


Clinical Photo of Palate ACC

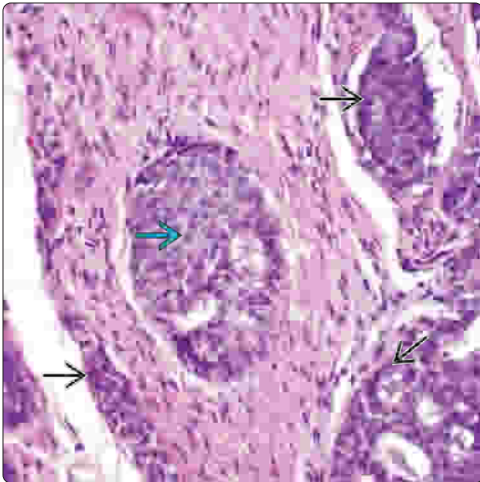
(Left) Clinical photograph shows a large ACC of the palate. The surface is ulcerated due to trauma while eating. This lesion was repeatedly treated as an infection before a biopsy revealed a solid variant of ACC. (Right) Gross photograph shows a multinodular focally circumscribed tumor of the parotid gland. The gross appearance of circumscription or encapsulation is not representative of the histologic findings of invasion.



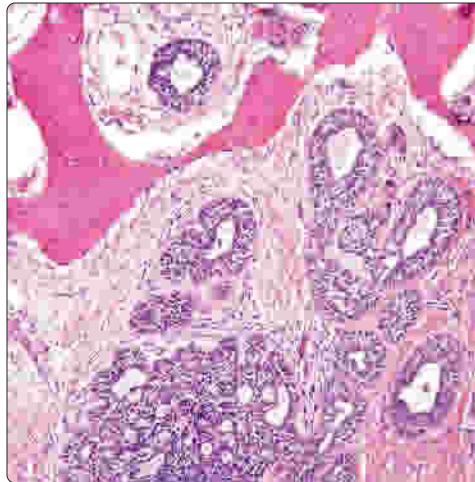
Multinodular Gross Appearance of ACC



Perineural and Intraneural Invasion

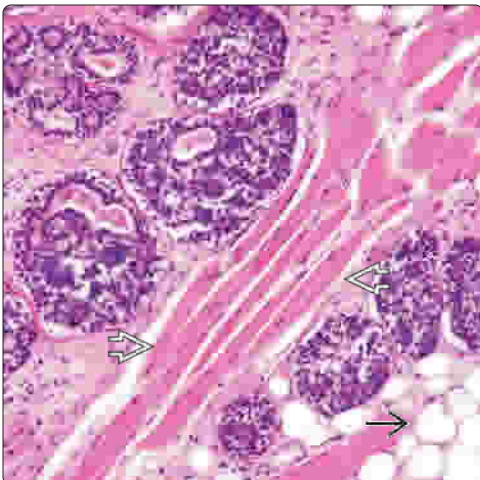


Destructive Bone Growth

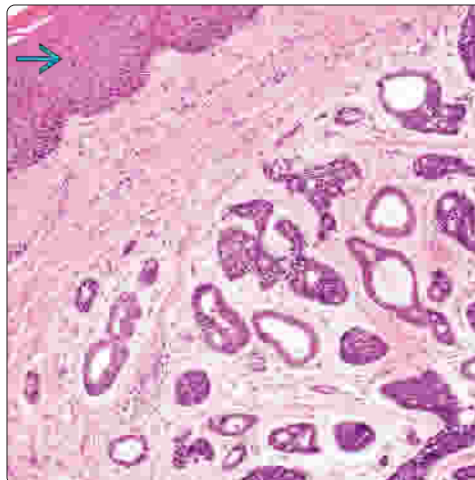


(Left) Intraneural and perineural invasion is a characteristic but not specific feature of ACC. Here a tumor island is seen within a nerve. Additionally, tumor nests are seen surrounding the nerve. (Right) The cells of ACC have invaded the bone of the palate, resulting in destructive growth. Tumors of the maxilla usually have a poor prognosis because they are close to vital structures, including the brain.

Skeletal Muscle Infiltration

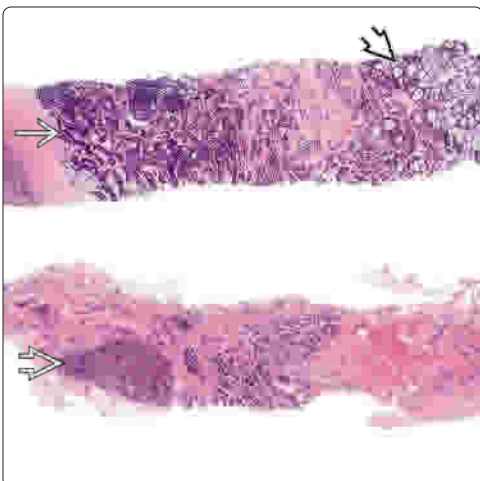


Tumor Below an Intact Epithelium

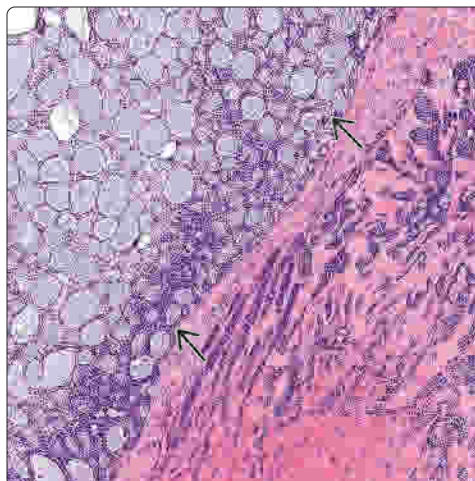


(Left) Tumor islands are seen infiltrating into the skeletal muscle and fat. Note the focal clear cell change within the proliferation. (Right) This image shows an ACC of the palate diagnosed in a middle-aged woman. While the overlying epithelium is intact, the mucosa is often ulcerated.



Core Needle Biopsy of ACC



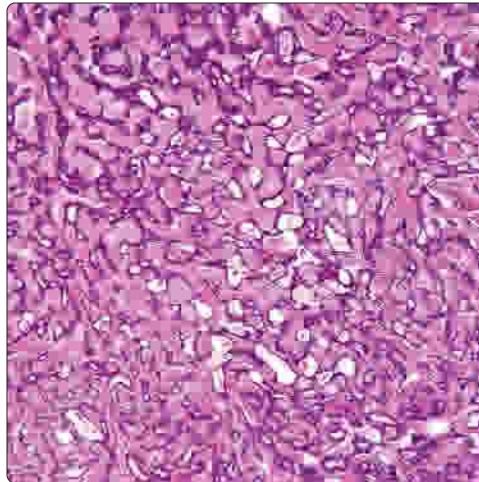
Multiple Patterns of Growth



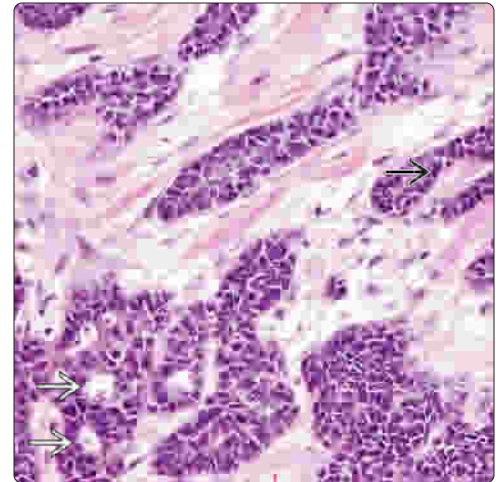
(Left) This needle biopsy of an ACC shows areas of solid, cribriform, and tubular patterns. Core biopsies can be difficult to confidently diagnose, but just knowing pre-therapy that there is a "malignant salivary gland neoplasm" may be helpful in guiding therapy. (Right) The classic cribriform pattern of ACC is identified immediately adjacent to areas of single-cell infiltration. This pattern can also be seen in polymorphous low-grade adenocarcinoma (PLGA). However, nuclear features help make the separation.

(Left) The tumor cells are set within a dense, brightly eosinophilic, hyalinized stroma. The stroma is composed of basal lamina. **(Right)** Ductal cells and lumina are more readily identified in the tubular pattern . The tumor cells focally surround eosinophilic material that is continuous with the intervening stroma . Different patterns are often mixed throughout a single tumor; however, a predominant tubular pattern is associated with a grade 1 tumor and a better 5-yr survival rate.

Hyalinized Stroma Compressing Glands

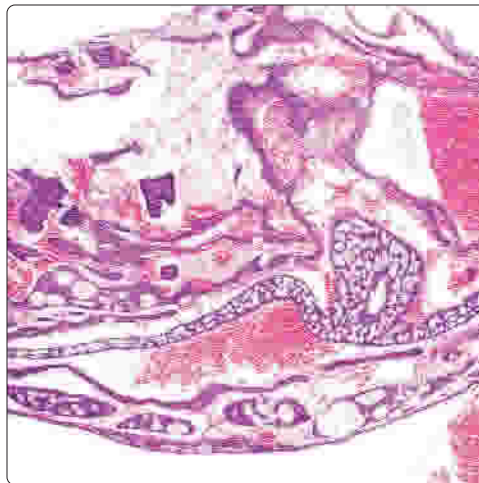


Tubular Pattern

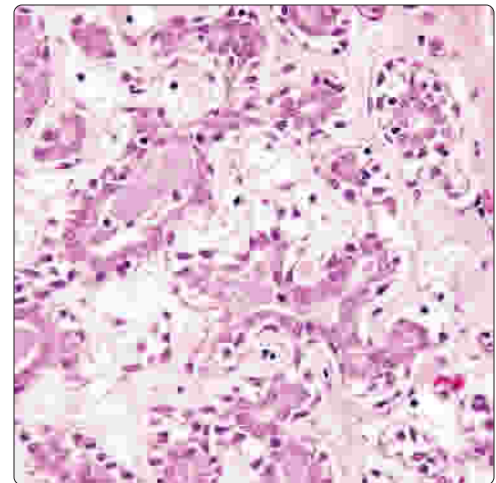



(Left) A low-power image shows an ACC with areas of variably sized cysts. A high-power view would show the typical cytology of an ACC. **(Right)** Clear cell change is noted within a myoepithelial focus in this ACC. This focus was found among areas that showed histologically characteristic features of ACC.

Cystic Adenoid Cystic Carcinoma

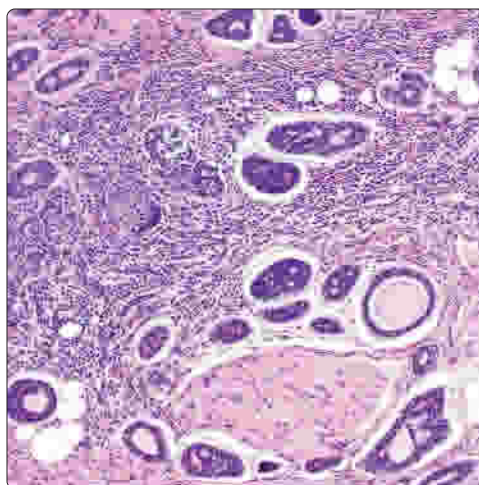


Clear Cell Changes

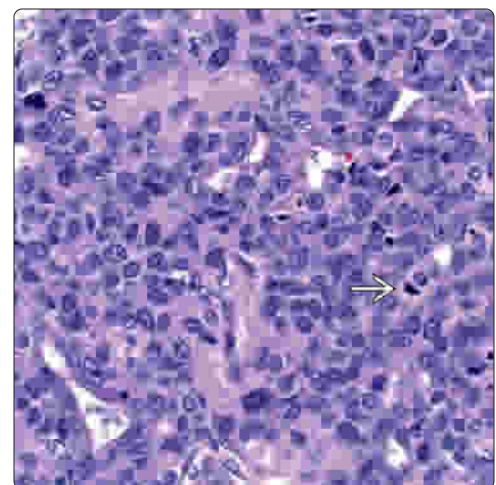


(Left) Tumor-associated lymphoid proliferation is a feature most often found around mucoepidermoid and acinar cell carcinomas but may be seen in other tumors, like this example of ACC. Inflammation may also contribute to secondary infection or ulcer of the adjacent mucosa. **(Right)** Hematoxylin and eosin shows a tumor with a solid pattern. This particular pattern tends to be more cytologically atypical, demonstrating pleomorphism and atypical mitotic figures .

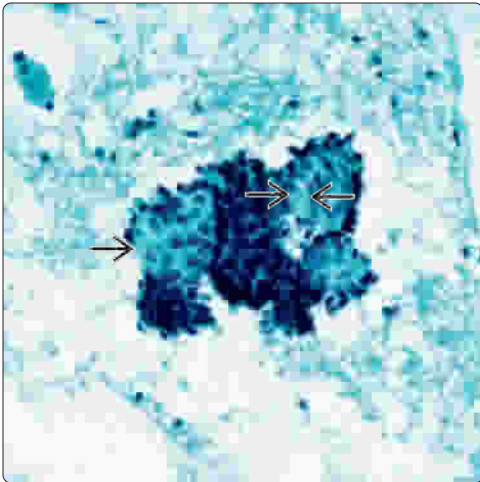
Tumor-Associated Lymphoid Proliferation



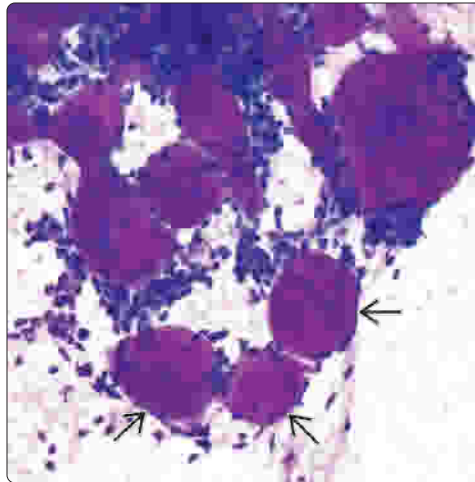
Solid Pattern of ACC



Hyaline Material

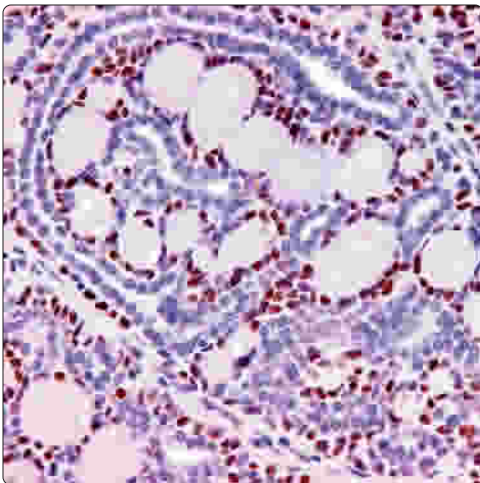


Bubblegum-Like Hyaline Spheres

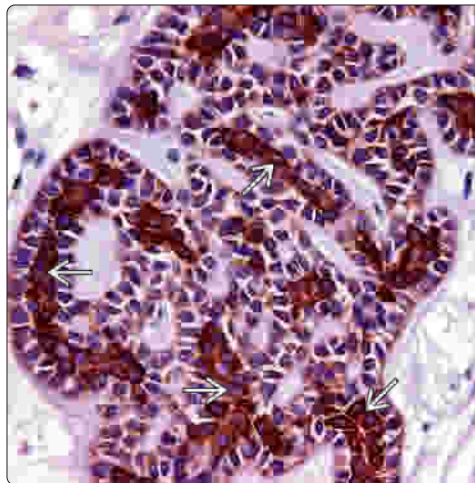


(Left) This Papanicolaou-stained fine-needle aspiration shows an aggregate of small round to oval cells with hyaline material that is clear to pale green [2]. Note the cells are surrounding the material. **(Right)** Diff-Quik stained (air-dried) fine-needle aspiration shows a cluster of cells with round nuclei and purple hyaline spheres [2]. These purple areas (bubblegum-like) are helpful in diagnosing ACC. The cells surround the hyaline material rather than merging with it, as would be seen in pleomorphic adenoma.

p63 Nuclear Reactivity

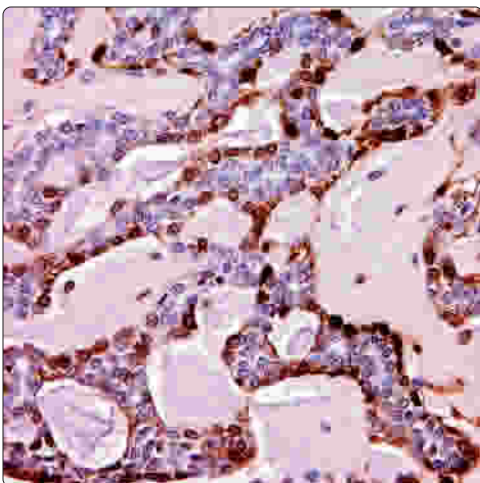


CK-PAN Reactivity

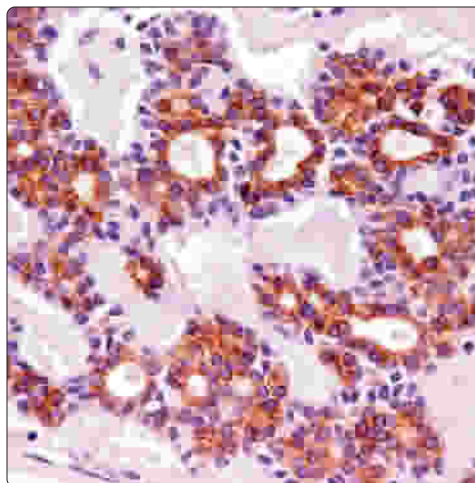


(Left) p63 shows strong nuclear reactivity in abluminal cells of ACC. The 2nd population of cells lacks reactivity, a feature that highlights the epithelial-myoepithelial phenotype of the tumor. **(Right)** CK-PAN shows cytoplasmic reactivity in this ACC. Staining intensity may vary among different tumors and even within a single neoplasm. This tumor shows more intense staining of the luminal cells [2].

S100 Protein Immunoreactivity



CD117 Immunoreactivity



(Left) S100 protein shows primarily nuclear reactivity in this ACC, but cytoplasmic staining is seen. S100 protein has variable nuclear and cytoplasmic reactivity and may show remarkable intensity among different tumors and even in the same tumor. **(Right)** CD117 (c-KIT) is consistently reactive in the cell membrane and cytoplasm of ACC, with the solid variant being more reactive than the tubular variant. Note the differential immunoreactivity, with luminal cells highlighted.

Acinic Cell Carcinoma

KEY FACTS

TERMINOLOGY

- Malignant neoplasm of serous acinar cell differentiation

CLINICAL ISSUES

- ~ 10% of all malignant salivary gland tumors
- Parotid gland most commonly affected (90%)
- Complete surgical excision is treatment of choice
- Generally good prognosis (5-year survival: 90%)
- Recurrences (locally) in ~ 35% of cases

MICROSCOPIC

- Circumscribed, solitary, oval to round masses
- Although one pattern and cell type often dominate, combination and spectrum is common
- **Patterns (in order of frequency)**
 - Solid/lobular, papillary-cystic, microcystic
 - Follicular is rare
- Multiple cell types

- **Serous acinar:** Large, polygonal cells, with abundant lightly basophilic granular cytoplasm
- **Intercalated duct type:** Smaller, eosinophilic to amphophilic cells
- **Vacuolated:** Clear, cytoplasmic vacuoles
- **Nonspecific glandular:** Round to polygonal, often syncytial, and smaller than acinar cells
- **Clear cells:** Nonstaining cytoplasm
- Associated with lymphoid infiltrate, sometimes prominent

ANCILLARY TESTS

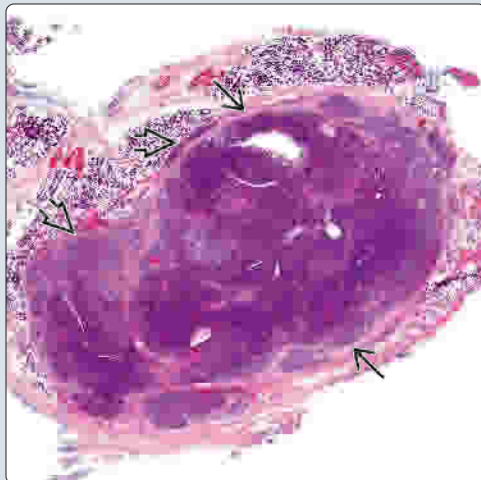
- PAS(+), diastase-resistant zymogen granules

TOP DIFFERENTIAL DIAGNOSES

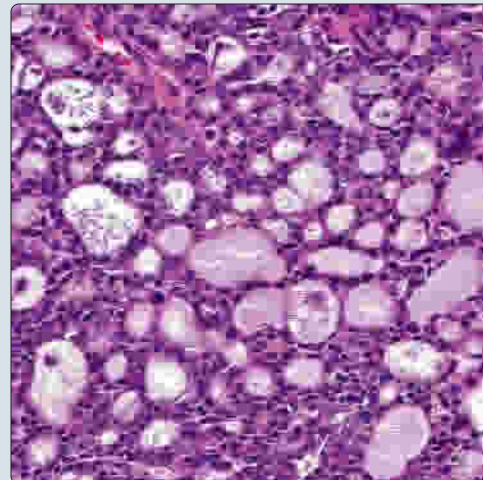
- Normal salivary gland
- Mammary analogue secretory carcinoma
- Papillary cystadenocarcinoma
- Metastatic thyroid carcinoma
- Clear cell tumors

Capsular Invasion

(Left) The tumors are usually circumscribed with an irregular periphery. This multinodular tumor has a suggestion of an incomplete fibrous connective tissue capsule surrounding it. Invasion into the parenchyma is noted. **(Right)** Acinic cell carcinoma (AcCC) shows multiple small cysts, creating a microcystic pattern. This lattice-like or sieve-like appearance is quite characteristic. There are secretions within the lumina of the cysts.

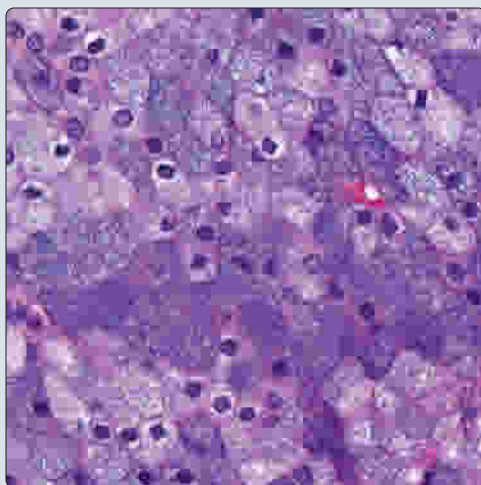


Microcystic Pattern

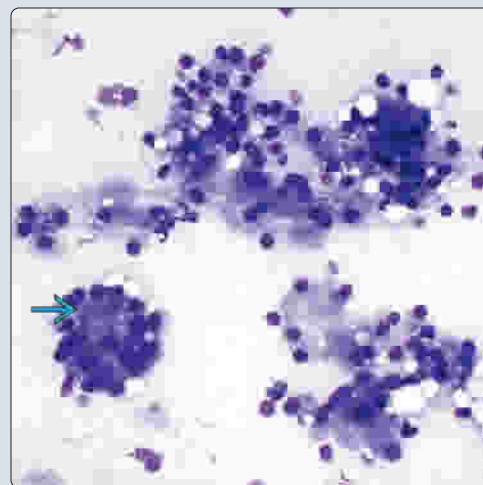


Blue-Dot Tumor

(Left) Serous acinar cells (most characteristic for AcCC) are large and polygonal with abundant light to dark basophilic, granular cytoplasm. Dense, blue to purple, fine to coarse zymogen granules are seen. **(Right)** Well-formed acinar units are noted in this fine-needle aspiration smear. There are focal granules in the cytoplasm, but the glandular and sheet-like appearance is more in keeping with a neoplasm than normal acini.



Cellular Clusters on Fine-Needle Aspiration



TERMINOLOGY

Abbreviations

- Acinic cell carcinoma (AcCC)

Synonyms

- Acinic cell adenocarcinoma
- Acinous cell carcinoma

Definitions

- Malignant epithelial salivary gland neoplasm demonstrating serous acinar cell differentiation with cytoplasmic zymogen secretory granules
 - Is **not** exclusively, nor even necessarily predominantly, serous-type cells
 - Salivary ductal cells are also part of this neoplasm

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Radiation exposure possible factor

Pathogenesis

- Serous acinar cell with zymogen secretory granules

CLINICAL ISSUES

Epidemiology

- Incidence
 - Accounts for ~ 6% of salivary gland tumors
 - Represents ~ 10-12% of all malignant salivary gland tumors
 - 2nd to mucoepidermoid carcinoma in frequency
- Age
 - Wide range
 - Even distribution from 2nd to 7th decades
 - Mean: Mid 40s
 - 2nd most common malignant salivary gland tumor in children (2nd decade)
- Sex
 - Female > male (2:1)

Site

- Parotid gland most common (90%)
 - Parotid is largest salivary gland, composed nearly exclusively of serous-type acini
- Submandibular (4%) and sublingual (1%)
 - Despite high serous type acini in sublingual gland
- Minor salivary glands rare
 - Intraoral, buccal mucosa, upper lip, and palate tumors are probably mammary analogue secretory carcinoma
- Most common bilateral salivary gland malignancy
 - Dwarfed by bilateral Warthin tumors and pleomorphic adenomas

Presentation

- History of slowly enlarging solitary parotid/facial mass, which may be mobile or fixed
 - Duration varies from weeks to several decades
- Pain (vague, intermittent) or tenderness is present in up to 1/2 of patients
- Facial nerve paralysis present in 5-10% of cases
 - Facial muscle weakness and tingling

Treatment

- Surgical approaches
 - Complete surgical excision treatment of choice
 - Incomplete excision portends poor prognosis
- Radiation
 - Not presently used in primary management
 - Improved survival for incompletely excised tumors or advanced stage disease
 - Valuable for occult metastases

Prognosis

- Generally, good prognosis
 - 5-year survival: 90% (disease specific)
 - ~ 8-10% die of disease (long median survival: ~ 30 years)
- Clinical stage more reliable than histologic grading in determining outcome
 - Stage I: No relapses or metastases
- Recurrences (locally) in ~ 35% of cases
 - Most develop within 5 years of diagnosis
- Mixed ductuloacinar tumors: lower relapse free survival than other types
- Poor prognosis (including tumor recurrence) associated with
 - Regional lymph node and distant metastases
 - Cervical lymph node metastases initially
 - Lung and bone most common distant sites (~ 15% of cases)
 - Multiple recurrences
 - Incomplete resection
 - Submandibular gland location or deep lobe of parotid involvement
 - Age > 45 years
 - Short symptom duration
 - Large size (> 3 cm)
 - Multinodularity
 - Histology: Cellular pleomorphism, necrosis, perineural invasion, stromal hyalinization, no lymphoid infiltrate, dedifferentiation
 - Increased mitoses (> 10% Ki-67 labeling)

MACROSCOPIC

General Features

- Circumscribed, solitary oval to round masses
 - Occasionally ill defined with irregular peripheries
 - Not usually encapsulated
 - Bilateral and multifocal tumors are rare
- Multinodularity is uncommon
- Cut surface is lobular and tan to red
- Rubbery to firm
- Solid to cystic (hemorrhagic)

Size

- Range: 0.5-13 cm
- Mean: 1-3 cm

MICROSCOPIC

Histologic Features

- Tumor extension into normal tissue is common, although apparent encapsulation is present

- Although one pattern and cell type often dominate, combination and spectrum is common
 - **Patterns (in order of frequency)**
 - Sheets, nodules, or aggregates in **solid/lobular** pattern (most readily recognized pattern)
 - **Blue dot tumor:** Basophilic, granular cytoplasm and round, basophilic nuclei
 - Small spaces in **microcystic** pattern
 - Yields lattice-like or sieve-like appearance
 - May represent coalescence of ruptured and degenerated vacuolated cells
 - Large cyst cavities with papillary projections of epithelial cells comprise **papillary-cystic** pattern
 - Due to complexity and sectioning, papillae appear to be floating within cystic spaces
 - Delicate fibrovascular cores are noted
 - Often vascular and hemorrhagic, with hemosiderin identified in cytoplasm of luminal cells
 - Luminal epithelial cells can have hobnail or tombstone row appearance
 - Usually intercalated duct-type and vacuolated cells
 - Multiple, epithelial-lined cystic spaces filled with eosinophilic proteinaceous material found in **follicular** pattern
 - Only prominent in ~ 5% of tumors
 - Usually intercalated duct-type cells
 - Psammoma bodies can be seen
 - Eosinophilic, homogeneous, proteinaceous fluid mimics thyroid colloid (hence follicular)
 - **Many cell types (in order of frequency)**
 - **Serous acinar** cells are large, polygonal cells with abundant lightly basophilic, granular cytoplasm
 - Strong resemblance to normal serous acini cells
 - Round, uniform, slightly eccentric nuclei, hyperchromatic to vesicular
 - Dense, gray to blue to purple, fine to coarse zymogen granules
 - Granules are often accentuated at lumen
 - Cytoplasm may be finely reticular or foamy
 - **Intercalated duct type** cells surround luminal spaces and tend to be smaller, eosinophilic to amphophilic cells
 - Cuboidal with centrally located nuclei
 - **Vacuolated** cells have clear cytoplasmic vacuoles
 - Majority cellular component in ~ 10% of tumors
 - Vacuoles fill most of cytoplasm, are variable in size, and tend to be smaller the greater the number present within cytoplasm
 - Vacuoles are negative with PAS and mucicarmine
 - Remaining cytoplasm is eosinophilic to amphophilic
 - **Nonspecific glandular** cells are round to polygonal, often syncytial, and smaller than acinar cells
 - Majority cellular component in ~ 15% of tumors
 - Amphophilic to eosinophilic cytoplasm with round nuclei
 - Granules are lacking
 - Nuclei are more variable
 - **Clear cells** have nonstaining cytoplasm with prominent cell borders
 - Present in ~ 6%; majority cellular component in < 1%
 - No glycogen identified (therefore, clearing is probably processing artifact)
 - Usually show small collections and are seldom dominant finding
 - Lymphoid infiltrate, sometimes prominent with germinal center formation (~ 40% of cases)
 - Tumor associated lymphoid proliferation
 - Sometimes it simulates lymph node but should not be misinterpreted as metastasis
 - Stromal fibrosis or desmoplasia is uncommon
 - High-grade transformation (dedifferentiation) into high-grade carcinoma is uncommon and heralds poor prognosis
- ## Variants
- Specific pattern is dominant or only finding
 - **Solid, microcystic, papillary-cystic, follicular**
 - Specific cell type is dominant or only finding
 - **Intercalated ductal, vacuolated cell, nonspecific glandular, and clear cell types**
- ## ANCILLARY TESTS
- ### Cytology
- High false-negative rate (interpreted as normal)
 - Cellular smears with clean background
 - Cohesive, small, tight clusters resembling normal acini
 - Fibrovascular core may be noted
 - Ducts and adipocytes are absent
 - Large, uniform cells with small, round, and regular nuclei with coarse chromatin (lymphocyte-like nuclei)
 - Serosus acinar cells with central nuclei
 - Ample, granular to vacuolated cytoplasm, lacking coarse granules
 - Stripped cytoplasm creates naked nuclei
 - Lymphocytes may be prominent component of stroma
- ### Histochemistry
- PAS(+), diastase-resistant zymogen granules
 - Reaction can be patchy and limited
 - No glycogen identified
 - Negative or only focally positive granules with mucicarmine
- ### Immunohistochemistry
- Immunoprofile is nonspecific and unpredictable, so seldom of diagnostic value
- ### Genetic Testing
- No consistent or specific structural chromosomal alterations
 - Deletions of chromosome 6q, loss of Y, and trisomy 21 reported
 - Loss of heterozygosity (LOH) most frequently at chromosomes 4p, 5q, 6p, and 17p
- ### Electron Microscopy
- Both acinar-type and ductal-type cells identified
 - Secretory zymogen granules in cytoplasm
 - Round, variably electron dense secretory granules
- ## DIFFERENTIAL DIAGNOSIS
- ### Normal Salivary Gland
- Lobular, with striated and interlobular ducts, acini, and adipocytes

Immunohistochemistry Table

Antibody	Reactivity	Staining Pattern	Comment
CK-PAN	Positive	Cytoplasmic	All tumor cells
α-1-antitrypsin	Positive	Cytoplasmic	Most tumor cells
α-1-antichymotrypsin	Positive	Cytoplasmic	Most tumor cells
DOG1	Positive	Cell membrane & cytoplasm	Intense apical, membranous &/or cytoplasmic reaction (complex)
CEA-M	Positive	Cytoplasmic	Many tumor cells
Amylase	Positive	Cytoplasmic	Weak and patchy (~ 10%), although positive in most tumors
LF	Positive	Cytoplasmic	Lactoferrin; positive in most tumors
S100	Positive	Nuclear & cytoplasmic	Seen in ~ 10% of tumors
α-amylase	Negative		Enzyme (+) in normal serous acinar cells but not in neoplastic cells
p63	Negative		
Calponin	Negative		
Actin-sm	Negative		
Mammaglobin	Negative		Used in the differential with mammary analogue secretory carcinoma
CK7	Negative		Negative in acinar/solid pattern; diffusely positive in ductal or papillary patterns

- Very well-differentiated tumors may be difficult to diagnose on core needle biopsy specimens

Mammary Analogue Secretory Carcinoma

- Uniform cells with vacuolated cytoplasm, microcystic to cystic and papillary architecture, intraluminal secretions, and scalloping
- Absence of basophilic granules
- Strong and diffuse reaction with mammaglobin, S100 protein, and CK7; *ETV6* translocation (+)

Papillary Cystadenocarcinoma

- Arranged in papillary and microcystic pattern
- Lacks zymogen granules, vacuolated cells, and intercalated ductal differentiation

Metastatic Thyroid Carcinoma

- Follicular pattern of AcCC mimics thyroid carcinoma
- Colloid, thyroglobulin (+) and TTF-1(+) confirm metastatic disease

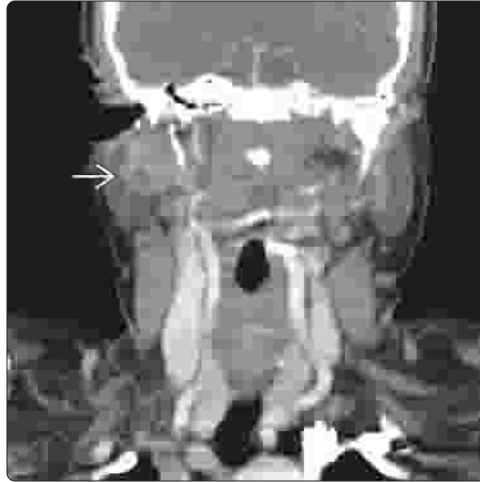
Clear Cell Tumors

- Clear cell variant of AcCC is rare, and clear cells are usually limited and focal
- Epithelial-myoeplithelial carcinoma: Usually biphasic, lacking serous acinar cell differentiation
- Clear cell adenocarcinoma: Associated with heavy fibrosis and strong glycogen content
- Clear cell oncocytoma: Oncocytes are present somewhere in tumor, with (+) mitochondrial stains
- Metastatic renal cell carcinoma: Shows pseudoalveolar pattern, prominent intercellular borders, significant glycogen, and usually pleomorphism

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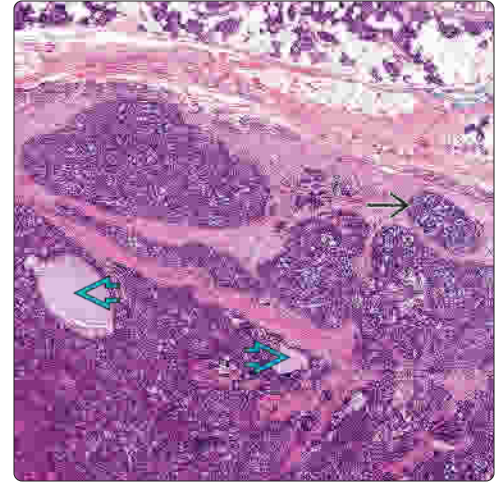
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CT: Mass



(Left) This CT image demonstrates a tumor mass in the right parotid gland [red box]. There is central degeneration or cyst formation. (Right) The periphery of the tumor is irregular, with a solid-lobular to nodular pattern. Areas suggesting vascular invasion [red box] are noted, but the separation from a nodule of tumor is sometimes challenging. Note the cysts within the tumor [blue box].

Irregular Tumor Periphery

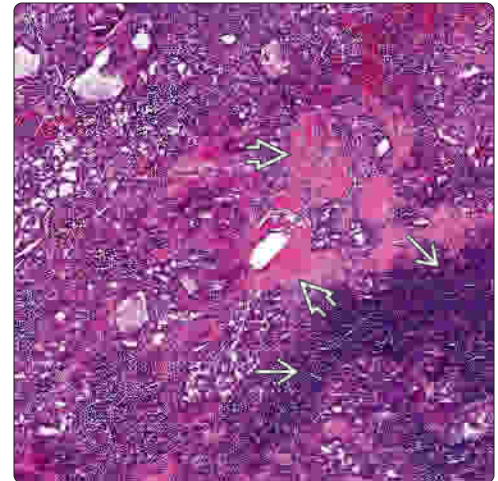


Bone Invasion Is Uncommon

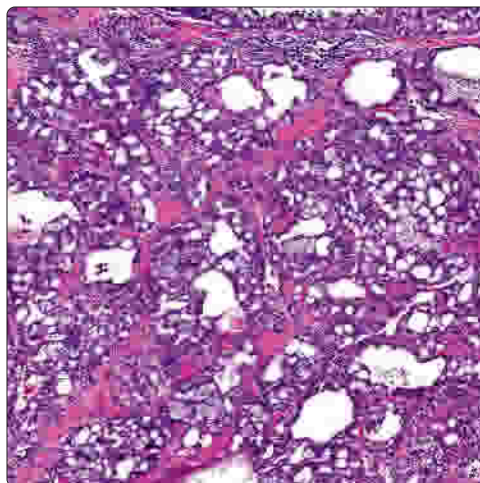


(Left) While infrequent, tumors may infiltrate into the adjacent bone [red box], as shown in this micrograph. The tumor islands are noted within the interstices of bone taken from the mandible. (Right) There are many times when there is a spectrum of patterns and cell types within a single tumor. In this case areas of solid, microcystic, and follicular architecture are seen, along with a prominent lymphoid infiltrate [red box]. Intratumoral fibrosis is easily identified [red box].

Multiple Patterns of Growth

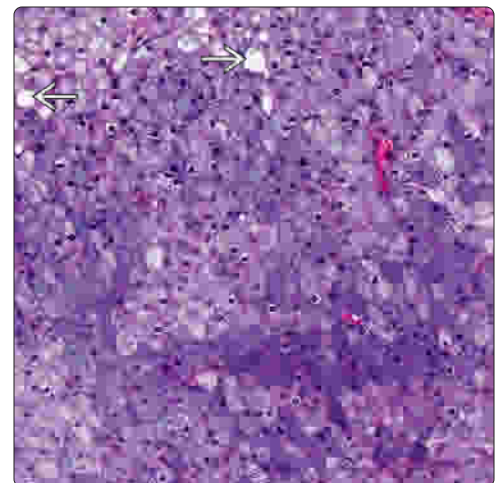


Microcystic Pattern

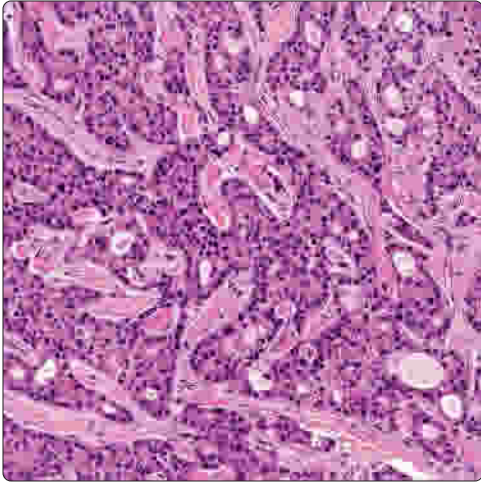


(Left) The microcystic appearance predominates in this AcCC. Fibrovascular septa are noted separating the tumor cells. Some of the cells are made up of the vacuolated cell type, further accentuating the cystic appearance. (Right) There are frequently slight variations in cytoplasmic appearance, where some cells have darker cytoplasm than others. However, these cells characterize serous acinar cells. There are a few foamy [red box] or finely reticular cells in this tumor.

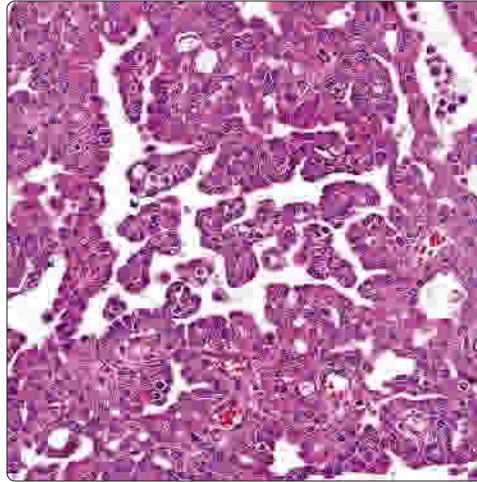
Serous Acinar Cells



Glandular Pattern With Fibrosis

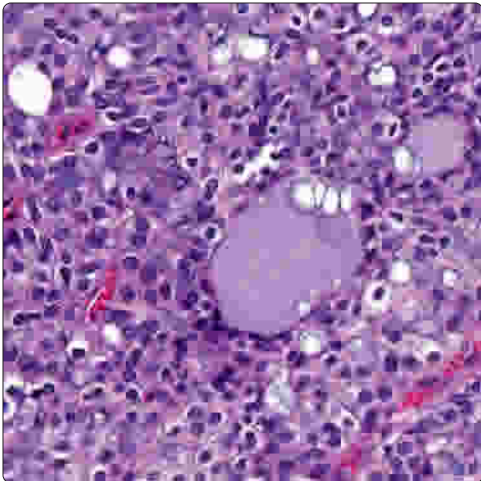


Papillary-Cystic Pattern

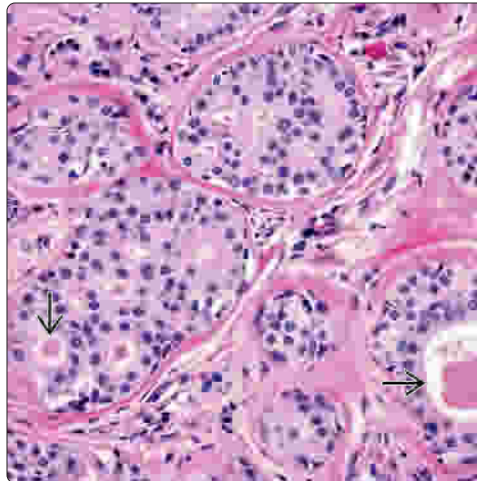


(Left) This tumor is arranged in a predominantly lobular and glandular pattern, with intratumoral fibrosis. The intercalated duct type cells are dominant in this tumor, with short cuboidal cells exhibiting central nuclei. **(Right)** The predominant pattern in this tumor is a papillary-cystic appearance. Some of the papillae have fibrovascular cores, while the majority do not.

Solid and Follicular Patterns

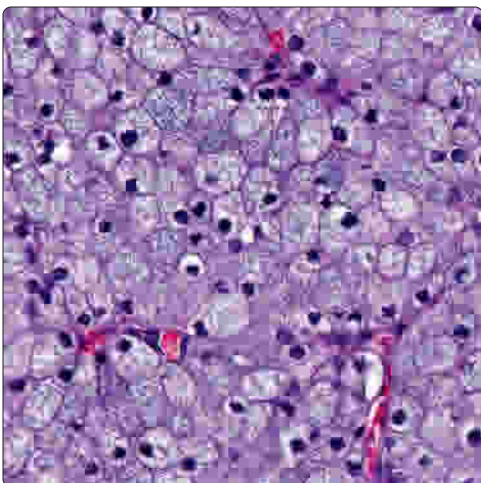


Follicular Pattern

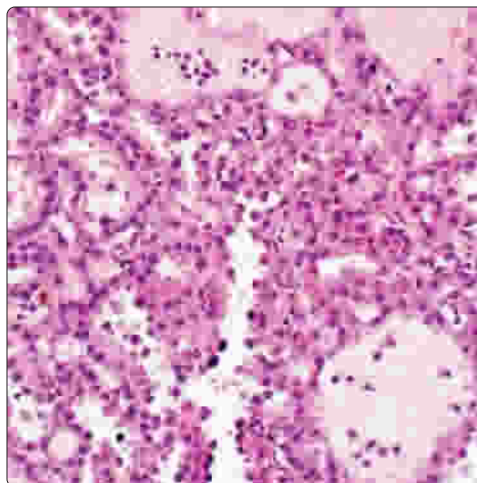


(Left) This field shows serous acinar cells as well as a few intercalated duct-type cells. Vacuolated cells are not identified in this case. There are secretions, a frequent finding in the follicular pattern. **(Right)** This tumor shows a follicular-type pattern. There are small, glandular-like cells arranged around the periphery of a gland, with concretions present in the center. The histologic similarity to a thyroid follicular tumor can be seen.

Serous Acinar Cells



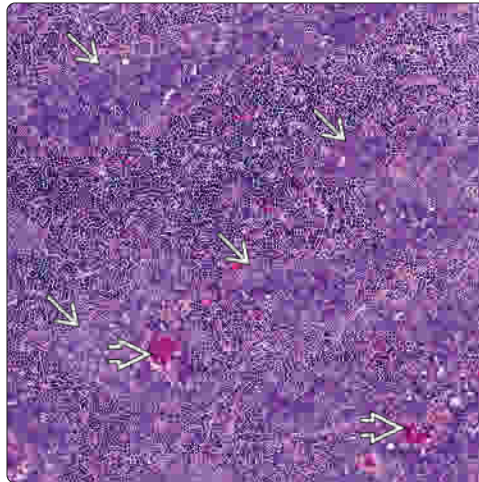
Papillary Cystic Pattern



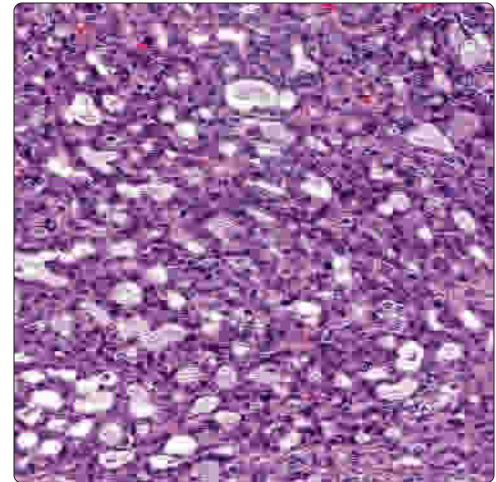
(Left) Abundant granular, basophilic cytoplasm is present in these serous acinar cells. The nuclei are hyperchromatic, round, and have a slightly eccentric placement within the cells. **(Right)** The papillary cystic pattern will often show a hobnail appearance to the neoplastic cells. The cytoplasm will occasionally contain hemosiderin material, picked up from hemorrhage.

(Left) The blending of the acinar cells with the background lymphoid elements is very subtle in this tumor. At low power, the epithelial elements may be inconspicuous, simulating the presence of a lymph node. There are secretions, which may help with the diagnosis of AcCC. **(Right)** This solid to microcystic tumor shows the nonspecific glandular cells that make up the tumor. There are no granules in the cytoplasm. This component can sometimes be quite prominent.

Tumor-Associated Lymphoid Proliferation

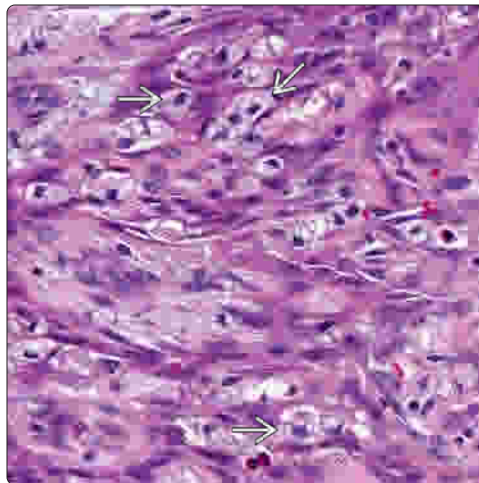


Glandular Cells

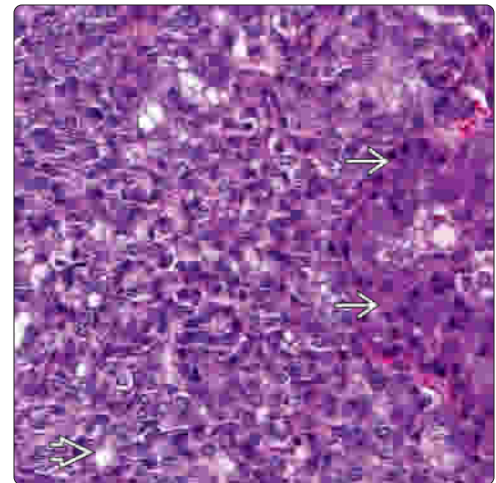


(Left) The acinar cells are surrounding a reactive metaplastic squamous proliferation. This is an uncommon reactive finding after fine-needle aspiration. The degree of cytologic atypia can be remarkable. **(Right)** High-grade transformation (dedifferentiation) can be seen in AcCC. In this case, the acinar cell component is juxtaposed to the sheet-like appearance of a poorly differentiated carcinoma. Subtle gland-like or duct-like profiles are noted.

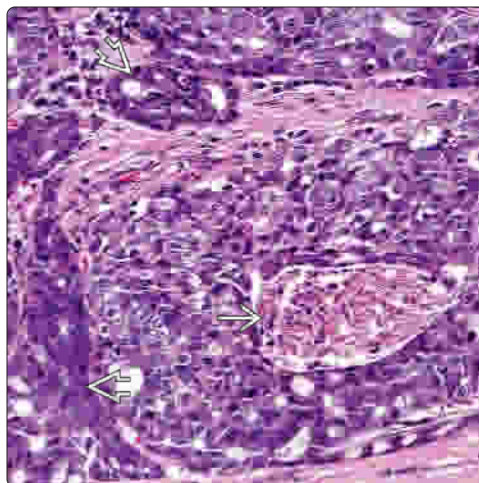
Squamous Metaplasia With Fibrosis



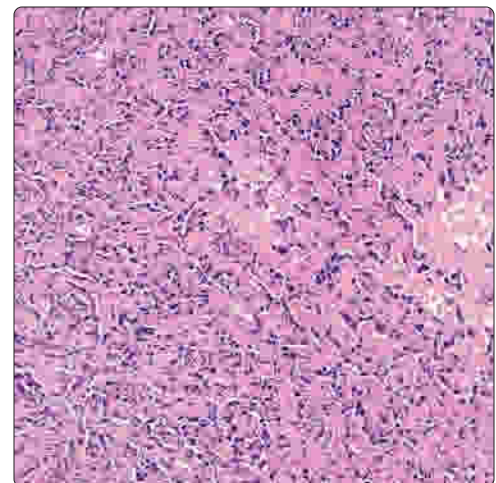
Dedifferentiation Into High-Grade Carcinoma



Tumor Necrosis in High-Grade Transformation

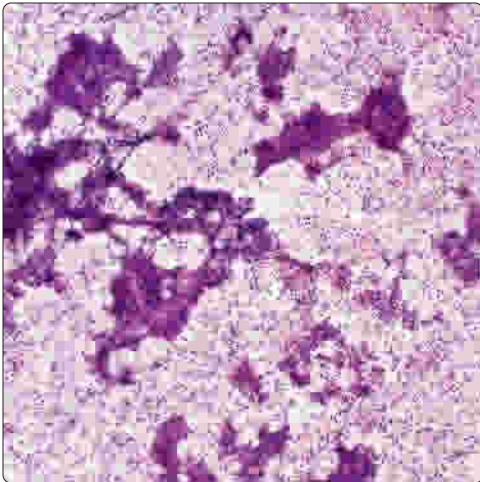


Heavy Stromal Fibrosis

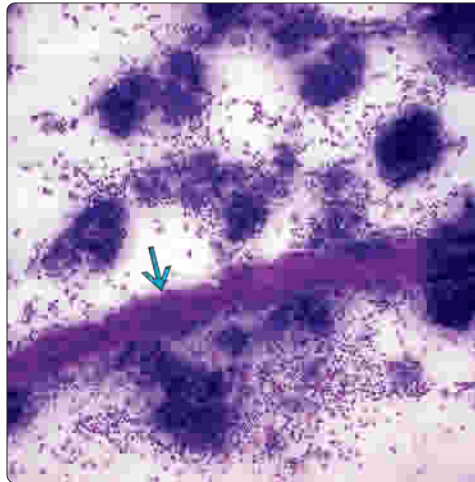


(Left) Higher grade tumors are frequently associated with areas of necrosis and degeneration. There are still multiple areas within the tumor that show the characteristic acinar cell appearance. **(Right)** This tumor is associated with a very dense stromal fibrosis. The fibrosis has compressed the neoplastic cells into cords and nests. At this magnification, a specific tumor type cannot be confirmed. However, the characteristic cellular components were present in other fields.

Cellular Smears

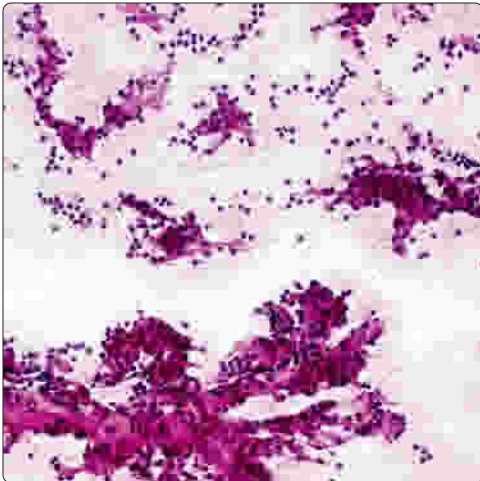


Cohesive Clusters on Fine-Needle Aspiration Smear

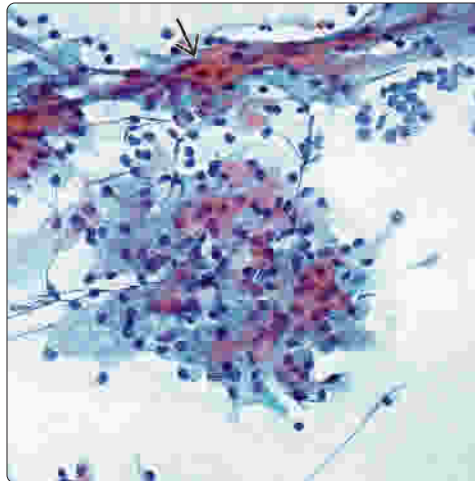


(Left) Smears from an AcCC can be remarkably cellular. Cohesive, small, tight clusters resembling normal acini are noted in a background of dispersed cells, showing stripped cytoplasm. **(Right)** There are numerous cohesive, tight clusters of acinar cells. There is a large fibrovascular core [2]. Ducts and adipocytes are absent, a feature helpful in excluding normal tissue.

Stripped Nuclei

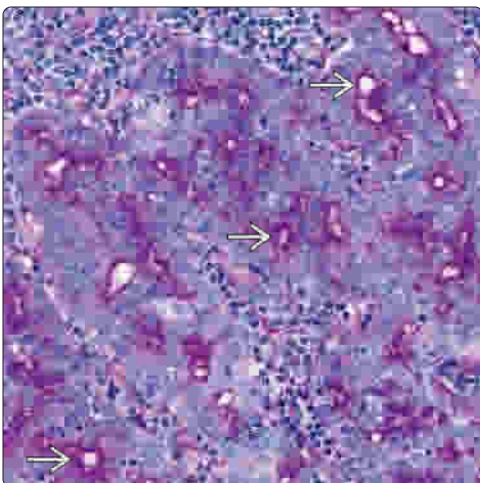


Acinar Cluster

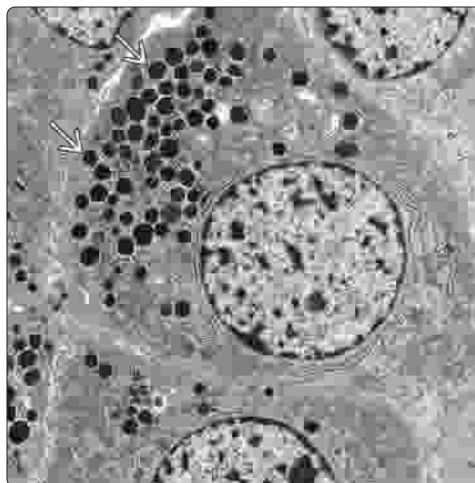


(Left) There is often a fine, granular background material, which represents the cytoplasmic content from cells that have been stripped of cytoplasm. The naked tumor cell nuclei can resemble lymphocytes. **(Right)** There are several acinar cells aggregated together without any intervening stroma or adipose tissue. Ductal epithelium is absent. There is a fibrovascular core [2].

Diastase-Resistant Zymogen Granules



Electron-Dense Zymogen Granules



(Left) PAS(+), diastase-resistant zymogen granules are accentuated at the lumina [2] in this AcCC. This pattern of distribution is quite common. **(Right)** An electron micrograph demonstrates the characteristic zymogen granules in the cytoplasm of a serous acinar cell. They are electron dense, showing slight variability in shape and size [2]. There are other cytoplasmic organelles, including mitochondria and endoplasmic reticulum. (Courtesy S. Bhuta, MD.)

Mammary Analogue Secretory Carcinoma

KEY FACTS

TERMINOLOGY

- Distinctive malignant tumor defined by t(12;15)(p13;q25) translocation resulting in *ETV6-NTRK3* fusion product

CLINICAL ISSUES

- Wide range (10-86 years)
- Males ~ females
- Parotid gland (~ 60%)
- Complete surgical excision yields good prognosis (similar to acinic cell carcinoma [AcCC])

MACROSCOPIC

- Solitary, circumscribed but not encapsulated

MICROSCOPIC

- Lobulated periphery with limited invasion
- Various patterns present, including microcystic, tubular, and solid
- Large cysts, tubular, follicular, and papillary structures

- Abundant, eosinophilic, homogenous, or bubbly secretions
 - Colloid-like material is present
- Uniform cells with bland vesicular nuclei with small nucleoli
- Pale to pink, granular or vacuolated apocrine-type cytoplasm

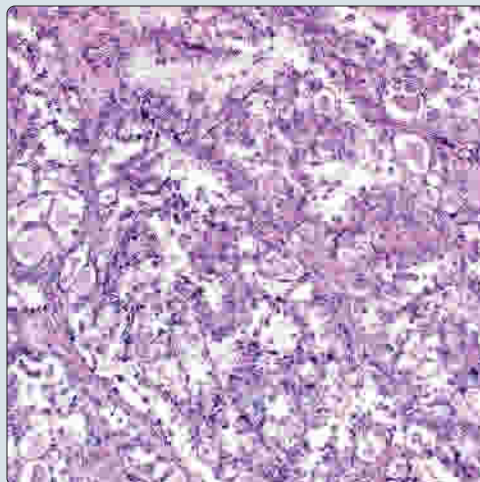
ANCILLARY TESTS

- Positive:** Mammaglobin, CK7, S100 protein, GATA3, STAT5a, GCDFP15, MUC1, MUC4
- Negative:** p63, CK5/6, DOG1, SMA, calponin, CK14
- FISH break-apart probe for *ETV6*

TOP DIFFERENTIAL DIAGNOSES

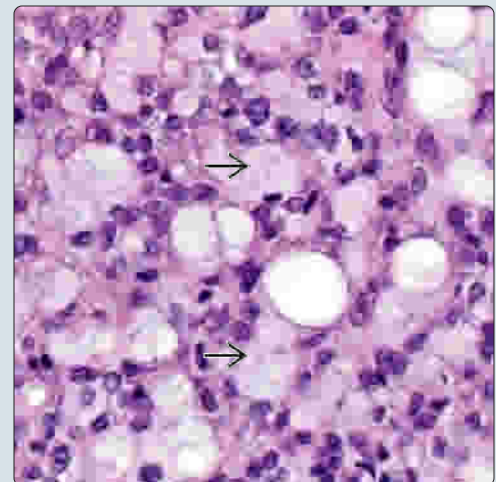
- Acinic cell carcinoma
- Polymorphous low-grade adenocarcinoma
- Papillary cystadenocarcinoma
- Adenocarcinoma, NOS (not otherwise specified)
- Mucoepidermoid carcinoma
- Low-grade cribriform cystadenocarcinoma

Papillary, Cystic, and Tubular Patterns

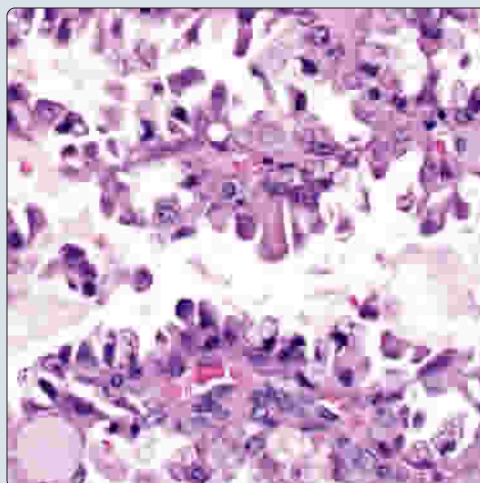


(Left) Mammary secretory analogue carcinoma (MASC) is often arranged in a variety of different patterns, with solid, papillary, and microcystic predominating. Secretions are easily seen throughout. (Right) The microcystic pattern is composed of monotonous cells arranged around abundant, eosinophilic to bluish bubbly secretory material [2]. The nuclear chromatin is delicate to vesicular.

Microcystic and Solid Pattern

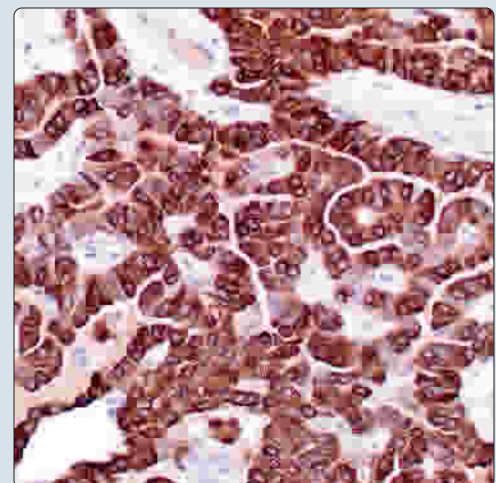


Hobnail Cells With Microvesicular Cytoplasm



(Left) MASCs may have a focal macrocystic or follicular architecture, with the cells projecting into the lumen showing a slightly hobnail appearance. There is finely vacuolated cytoplasm. (Right) Although positive in other salivary gland tumors, mammaglobin shows a consistent positive reaction in MASC. This case shows a strong and diffuse reaction, but the reaction may be focal and patchy.

Mammaglobin Reaction



TERMINOLOGY

Abbreviations

- Mammary analogue secretory carcinoma (MASC)

Synonyms

- Secretory carcinoma (WHO term)

Definitions

- Distinctive low-grade malignant tumor morphologically similar to breast secretory carcinoma, characterized by specific *ETV6* rearrangement
 - Zymogen granule poor acinic cell carcinomas (AcCC) are usually MASC

ETIOLOGY/PATHOGENESIS

Similar to Secretory Breast Carcinoma

- Morphologic and molecular resemblance between tumors
- Both show lactation-like secretory differentiation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon, but may be underreported or recognized as it was only recently described
- Age
 - Wide range (10-86 years)
 - Mean: 5th decade
- Sex
 - Males ~ females

Site

- Parotid gland (~ 70%)
- Minor salivary gland sites account for remainder: Oral (19%)
 - > submandibular (7%)
 - Lip, soft palate, and buccal mucosa

Presentation

- Slow-growing painless mass
- Neck lymph node metastases in up to 20% at presentation

Treatment

- Surgical approaches
 - Complete surgical excision
 - Neck dissection for clinically detected metastases
- Adjuvant therapy
 - Tyrosine inhibitors may be employed (used for *ETV6*-*NTRK3*[+] leukemias)

Prognosis

- Good overall, similar to AcCC
- Mean disease-free survival: ~ 7.5 years (like AcCC)

MACROSCOPIC

General Features

- Solitary, circumscribed but not encapsulated
- Rubbery, white-tan to gray cut surface
- May be cystic with yellow-white fluid

Size

- Mean: 1.7 cm (range: 0.2-5.5 cm)

MICROSCOPIC

Histologic Features

- Lobulated, nonencapsulated periphery with limited invasion
 - Extension into glandular tissues
 - Perineural invasion uncommon
 - Lymphovascular invasion rare
- Various patterns present, including microcystic, tubular, and solid
 - Large cysts, tubular, follicular, and papillary structures
- Abundant, eosinophilic, homogeneous, or bubbly secretions
- Colloid-like material is present
- Lacks secretory zymogen granules
- Similar to intercalated duct cells in acinic cell carcinoma
- Uniform cells with bland vesicular nuclei with small nucleoli
 - Finely granular chromatin
- Pale to pink, granular or vacuolated apocrine-type cytoplasm
- Mitoses are infrequent (< 3/10 high-power field [HPF])
- Necrosis usually absent
- Heavy fibrous septa with hyalinization seen in non-*NTRK3* fusion cases
- High-grade transformation is rare
 - High-grade component revealed strong membrane staining for EGFR and β -catenin, cytoplasmic/nuclear staining for S100 protein, and nuclear staining for cyclin-D1, whereas HER-2/neu was absent
 - May only have *ETV6* gene rearrangement and not fusion product

ANCILLARY TESTS

Cytology

- Highly cellular smears
- Cellular fragments of various size with singly dispersed cells
 - Small, loose to tight clusters of epithelial cells
 - Papillary groups showing transgressing vessels
- Mild to focally moderate nuclear atypia
- Naked nuclei (stripped of cytoplasm) may be seen
- Abundant cytoplasm, with fine granularity, showing vacuolization (small to large, occasionally multivacuolated)
- Mucinous to granular eosinophilic background debris
- Lacks: Ductal or acinar cells, epidermoid cells, tumor necrosis

Histochemistry

- Colloid-like secretory material stains positively for periodic acid-Schiff with and without diastase, Alcian Blue
- Lacks secretory zymogen granules

Immunohistochemistry

- **Positive:** Mammaglobin, CK7, S100 protein, STAT5a, GCDP15, MUC1, MUC4, GATA3
- **Negative:** p63, CK5/6, DOG1, SMA, calponin, CK14

In Situ Hybridization

- FISH break-apart probe for *ETV6*

Immunohistochemistry Table

Antibody	Reactivity	Staining Pattern	Comment
Mammaglobin	Positive	Cell membrane & cytoplasm	Strong, diffuse
S100	Positive	Nuclear & cytoplasmic	Strong, diffuse
GCDPF-15	Positive	Cytoplasmic	Strong, but focal, highlighting secretory material
pSTAT5	Positive	Nuclear	Strong reaction
GATA3	Positive	Nuclear	Strong, diffuse in most tumor cells
CK7	Positive	Cytoplasmic	Strong, diffuse
Vimentin	Positive	Cytoplasmic	Strong, diffuse reaction
CK-PAN	Positive	Cytoplasmic	Strong, diffuse reaction
CK8/18/CAM5.2	Positive	Cytoplasmic	
Adipophilin	Positive	Cytoplasmic	Large lipid droplets
p63	Negative		May show cytoplasmic reaction in lipid-rich cells
Calponin	Negative		
CK5/6	Negative		
DOG1	Negative		Acinic cell carcinoma shows strong apical-membranous staining
Ki-67	Positive	Nuclear	Usually < 5% proliferation index

Genetic Testing

- Recurrent balanced t(12;15) (p13;q25) chromosomal translocation resulting in *ETV6-NTRK3* fusion product
 - ETV6* gene on chromosome 12
 - NTRK3* on chromosome 5
- RT-PCR detection of *ETV6-NTRK3* fusion transcript
- Transcription regulator (*ETV6*) fuses with membrane receptor kinase (*NTRK3*), activates kinase, and promotes cell proliferation and survival

DIFFERENTIAL DIAGNOSIS

Acinic Cell Carcinoma

- Growth pattern diversity similar to MASC
- Mixture of serous acinar, intercalated duct-like, hobnail, vacuolated, clear, and nonspecific glandular cells
- Dark blue cytoplasmic zymogen granules
- Mammaglobin (-) and DOG1(+)

Polymorphous Low-Grade Adenocarcinoma

- Positive:** S100 protein, mammaglobin, but also p63, GFAP, and actins

Papillary Cystadenocarcinoma

- Papillary architecture unassociated with bubbly secretions
- Pleomorphism, with necrosis and increased mitoses

Mucoepidermoid Carcinoma

- Combination of transitional cells and mucocytes
- Cobblestone appearance with well-defined cell borders and squamoid areas
- Strong and diffuse p63 and CK5/6 immunoreactivity

Low-Grade Intraductal Carcinoma

- Usually shows cribriform pattern with in situ architecture showing myoepithelial cells lining cysts

- Positive:** S100 protein; p63(+) basal cells surround tumor nests

Adenocarcinoma, Not Otherwise Specified

- Diagnosis of exclusion

Cystadenoma

- Morphologic overlap, but bubbly secretions, vacuolated cytoplasm, and IHC profile makes separation

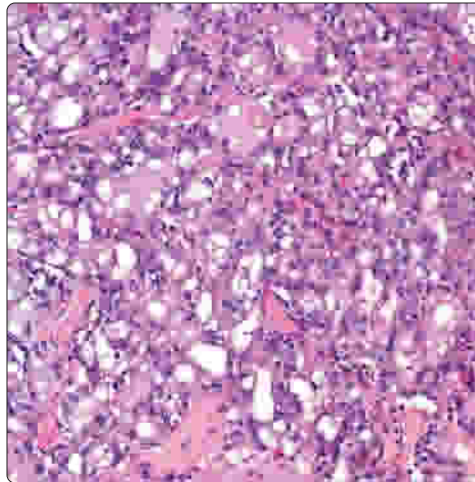
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Circumscribed Tumor Periphery

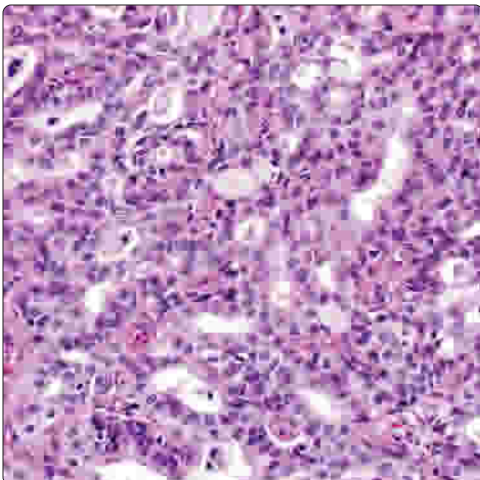


Microcystic Pattern With Bubbly Secretions

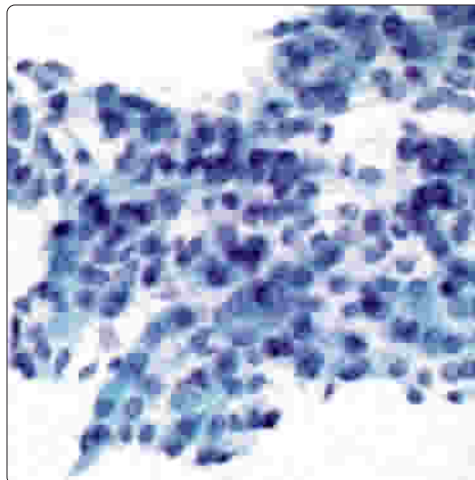


(Left) There is a well-defined periphery, focally associated with lymphoid aggregates. Extension into the adjacent parenchyma is seen. Fibrous septa are separating the tumor into nodules. (Right) Microcystic to solid and tubular structures are seen in most cases of MASCC. Note the bubbly secretions, creating an open appearance.

Solid and Tubular Patterns

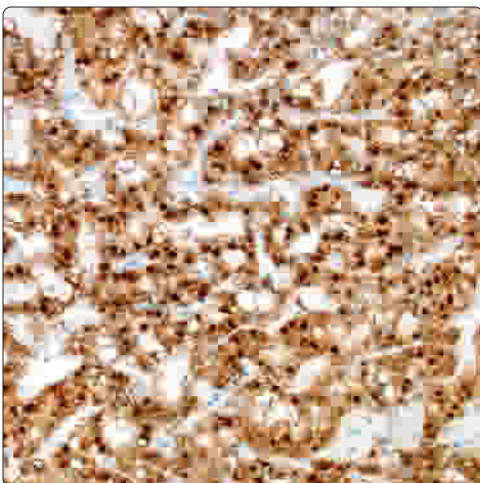


Disorganized Cluster

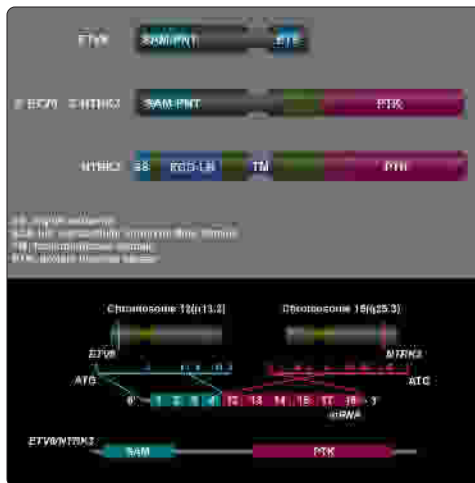


(Left) The secretions are seen within the central portions of the tubular structures. These secretions are positive with alcian blue and PAS \pm diastase (not shown). (Right) There is a loosely cohesive, disorganized cluster of neoplastic cells in this MASCC smear. Note the moderate, finely granular to bubbly cytoplasm surrounding round, uniform nuclei with small dark nucleoli. These cells mimic histiocytes.

S100 Protein (+) Tumor Cells



ETV6-NTRK3 Translocation



(Left) The neoplastic cells show a diffuse and strong nuclear and cytoplasmic reaction with S100 protein. (Right) This graphic demonstrates the chromosome location that results in the characteristic ETV6/NTRK3 fusion, unique in salivary gland neoplasms.

KEY FACTS

TERMINOLOGY

- Malignant epithelial tumor characterized by infiltrative growth of cytologically uniform cells arranged in architecturally diverse patterns

CLINICAL ISSUES

- 2nd most common intraoral minor salivary gland malignant tumor (~ 25%)
- Female > male (2:1)
- Almost **always** in minor glands (palate: 60%)
- Usually forms slow-growing, firm, nontender mass
- Complete, but conservative surgical excision is treatment of choice
- Overall excellent long-term prognosis

MICROSCOPIC

- Unencapsulated, although well circumscribed
- Infiltrative growth
 - Incarcerated minor salivary glands

- Significant perineural invasion
- Striking variety of growth patterns
 - Eye of the storm or whorled appearance
 - Concentric layering of cells around central nidus, creating **targetoid** tableau
- Uniformly bland round to polygonal or fusiform tumor cells
- Slate blue-gray stroma usually only focal
- Mitoses are infrequent

ANCILLARY TESTS

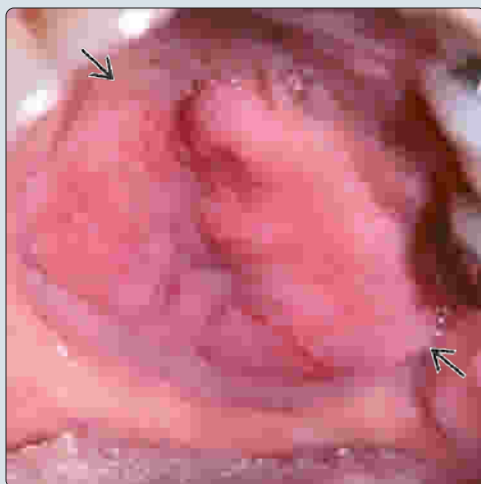
- Expression of epithelial and myoepithelial markers

TOP DIFFERENTIAL DIAGNOSES

- Pleomorphic adenoma
- Adenoid cystic carcinoma
- Papillary cystadenocarcinoma
- Cribriform adenocarcinoma of minor salivary glands

(Left) Clinical photo demonstrates a palate mass [X]. The overlying mucosa exhibits a rough or stippled appearance, a feature that is seen more frequently in polymorphous low-grade adenocarcinoma (PLGA) than other tumor types. (Courtesy B.W. Neville, DDS.) **(Right)** PLGA often shows a number of different patterns of growth, as seen in this case. Eye of the storm or hurricane swirling is characteristic. Note that the minor salivary glands [X] are encased by the neoplastic cells.

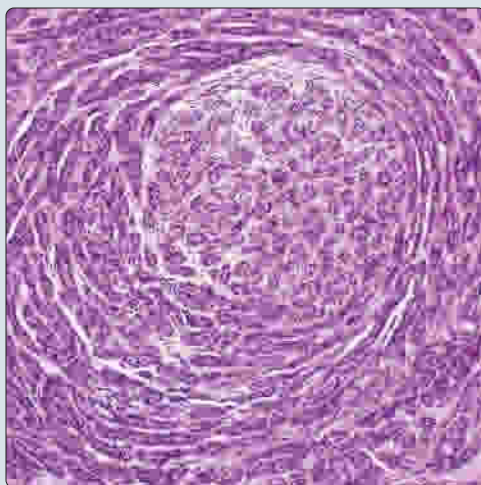
Stippled (Rough) Mucosa Over PLGA



Eye of the Storm Pattern

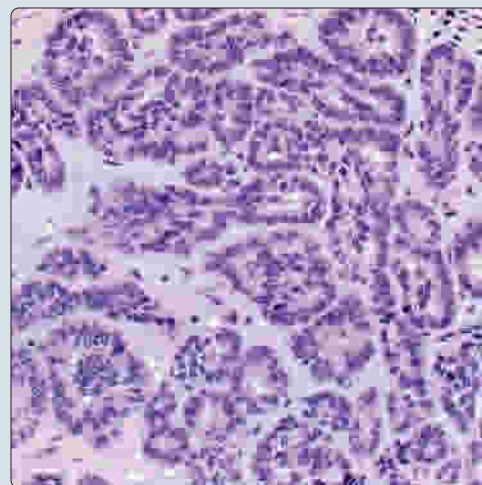


Targetoid Perineural Involvement



(Left) The center of the target is often a nerve, as seen in this case. The neoplastic cells stream out and create a whorled appearance. This is quite characteristic of PLGA. **(Right)** The neoplastic cells are separated by a characteristic slate blue-gray stroma. Note the very fine nuclear chromatin in nuclei that are monotonously round and regular.

Slate Blue-Gray Stroma



TERMINOLOGY

Abbreviations

- Polymorphous low-grade adenocarcinoma (PLGA)

Synonyms

- Terminal duct carcinoma
- Lobular carcinoma

Definitions

- Malignant epithelial tumor characterized by infiltrative growth of cytologically uniform cells arranged in architecturally diverse patterns
- Cribriform adenocarcinoma of minor salivary glands (CAMSG) considered variant of PLGA

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Intercalated/terminal duct derivation is presumptive

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon: ~ 2% of all salivary gland tumors
 - 2nd most common intraoral minor salivary gland malignant tumor (~ 25%)
- Age
 - Wide range: 16-95 years
 - Mean: 60 years
 - Vast majority are 50-70 years
 - Exceedingly rare in children
- Sex
 - Female > male (2:1)
- Ethnicity
 - Predilection for black patients

Site

- Almost **always** in minor glands
- Order of frequency
 - Palate (60%), especially at mucosal junction of hard and soft palates
 - Buccal (cheek) mucosa (~ 15%)
 - Lip (particularly upper) (~ 10%)
 - Retromolar areas
 - Floor of mouth, tongue (posterior 3rd specifically), oropharynx, tonsil
 - Other sites: Lacrimal gland, sinonasal tract, nasopharynx, and upper/lower respiratory tracts
- Multifocal synchronous primaries are rare

Presentation

- Usually forms slow-growing, firm, nontender mass
 - "Dentures not fitting"
- Discovered incidentally during routine dental examination
- Ulceration, bleeding, or telangiectasia and pain are uncommon
- Bone erosion or infiltration is uncommon
- Tumors may be mobile or fixed
- Neck mass rarely seen in patients with floor of mouth tumors

- Duration of symptoms varies from few days up to 40 years
 - Mean: 2 years

Treatment

- Options, risks, complications
 - Long-term clinical follow-up is warranted due to indolent nature and prolonged latent period
- Surgical approaches
 - Complete, but conservative surgical excision is treatment of choice
 - Incisional biopsy is often initial diagnostic procedure
 - Wide excision due to frequent perineural invasion
 - Neck dissection for proven regional metastases
- Radiation
 - Uncommonly, postoperative radiation used for recalcitrant recurrences
 - Palliative rather than curative

Prognosis

- Overall excellent long-term prognosis
 - ~ 95% 10-year survival
 - Patients may die **with** tumor, but generally not **from** tumor
- Local recurrences in 9-15% of cases
 - Hard palate tumors especially
 - Recurrences may develop many years after primary (mean: 5-7 years)
 - Women are more likely to develop recurrences than men
- Spread to regional lymph nodes in 9-15% of cases
 - Increased risk of metastases with positive surgical margins
- Distant metastases are rare
 - Lung is most commonly affected site

IMAGING

Radiographic Findings

- Radiographs performed for mucosal tumors overlying bone to determine extent of surgery

MACROSCOPIC

General Features

- Uniformly firm to solid, ovoid masses
- Characteristically unencapsulated, although well circumscribed
- Tumor approximates overlying surface mucosa, which is seldom ulcerated
- Cut surface is homogeneous, pale-yellow to tan

Size

- Range: 0.4-6 cm; mean: 2 cm
- Lip tumors tend to be smaller
 - Lip tumors are more easily detected clinically when smaller rather than representing an innate difference in biology
- Size does not influence prognosis

MICROSCOPIC

Histologic Features

- Infiltrative growth, architectural diversity, and cytologic uniformity, set in characteristic matrix

Polymorphous Low-Grade Adenocarcinoma

- **Infiltrative** growth
 - Unencapsulated, but usually well circumscribed
 - Uninvolved, usually intact surface epithelium
 - Encased, entombed, incarcerated, or completely surrounded minor salivary glands, with wrapping around, but not destruction by neoplastic cells
 - Invades into soft tissues, especially fat; less frequently skeletal muscle
 - Significant perineural invasion
 - Bone invasion is seen, especially with palate tumors
- **Patterns** of growth
 - Striking variety of growth patterns
 - Low power gives eye of the storm, streaming, or whorled appearance
 - Characteristic concentric layering of cells around central nidus, creating targetoid tableau
 - Nidus formed by small nerve twigs
 - Periphery often shows linear, single-file cell infiltration
 - Arranged in lobules, thèques, glandular profiles, tubules, trabeculae, and cribriform nests
 - Interconnecting cords parallel to more solid, convex nests of tumor
 - Small tubules lined by single layer of cuboidal cells
 - Papillae, if identified, are focal and not dominant pattern
- **Cellular** features
 - Uniformly bland (isomorphic) round to polygonal or fusiform tumor cells
 - Small to medium, with indistinct cellular borders
 - Ample pale to eosinophilic cytoplasm
 - Round to oval nuclei with open, vesicular nuclear chromatin
 - Inconspicuous to small nucleoli
- **Matrix** material
 - Slate blue-gray stroma usually only focal
 - Hyalinized, slightly eosinophilic stroma separates cells
- Inconspicuous mitoses
- Tyrosine-like crystals are uncommonly identified (< 5%)
- Necrosis is rare
- Rare metaplastic changes: Squamous, sebaceous, mucous, clear, oncocytic
- Some believe **cribriform adenocarcinoma of tongue** may be variant of PLGA
 - Doubtful, as there is high frequency of regional lymph node metastases

ANCILLARY TESTS

Cytology

- Limited experience, as minor salivary gland tumors are infrequently sampled
- Cellular smears with cuboidal and spindle cells in sheets or small groups
- Bland, round or oval nuclei with fine chromatin, lacking nucleoli
- Myxoid stromal fragments and hyaline globules similar to pleomorphic adenoma
 - Tumor cells surround stroma

Immunohistochemistry

- Variable expression of epithelial and myoepithelial markers
 - Differences in number of cells reactive and intensity

Genetic Testing

- Recurrent hotspot activating *PRKD1* mutation (p.Glu710Asp, exon 15) in ~ 75% of tumors
- Chromosome 12 abnormalities are most common: p or q arms (12q22 and 12p12.3)
 - t(6;12)(p21;q13) and t(6;9)(p21;p22) also noted
- Genome-wide, high-resolution aCGH analysis demonstrated few copy number alterations (CNAs)
- Rarely, *MYB-NFIB* gene fusion detected or *PRKD2* rearrangements

Electron Microscopy

- Tumor cells are well-differentiated myoepithelial cells (fusiform cells with electron-lucent cytoplasm) separated by excess basal lamina and glycosaminoglycans
- Transitions from myoepithelial cells to luminal epithelial cells with intraluminal microvilli

DIFFERENTIAL DIAGNOSIS

Pleomorphic Adenoma (PA)

- Very difficult with small biopsies
- Minor salivary gland PAs are **not** encapsulated but are nodular or bosselated
- Lack perineural invasion
- Plasmacytoid cells are common but lacking in PLGA
- Myxochondroid matrix usually present (except in cellular tumors)
 - Both have hyaline or mucohyaline stroma
- Strong and diffuse GFAP seen in epithelial cells and in mesenchymal cells
 - PLGA shows faint, focal, or weak reactivity in epithelial luminal cells only

Adenoid Cystic Carcinoma (ACC)

- Multiple growth patterns mimic PLGA, although cribriform pattern much more common in ACC
 - Fascicular pattern is not seen in ACC
- Nuclei are peg-shaped, carrot-shaped, or angular, with hyperchromasia
- Pseudocystic spaces with glycosaminoglycans
 - Slate blue-gray background matrix is not seen
- Proliferation index usually higher than PLGA

Papillary Cystadenocarcinoma

- Papillary pattern is dominant
- Tumor is cystic, while this is not true of PLGA
- More frequently with pleomorphism and mitoses

Cribriform Adenocarcinoma of Minor Salivary Glands

- Cribriform architecture with invasive periphery
- Very monotonous nuclei with delicate, vesicular to open nuclear chromatin (like thyroid papillary carcinoma)
- High frequency of metastases
- Unique *PRKD* gene alterations different from PLGA

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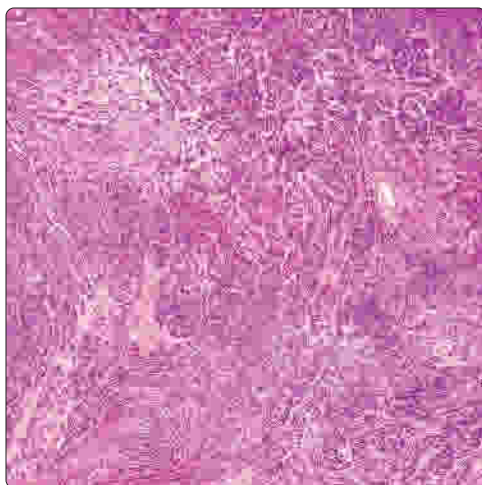
Immunohistochemistry Table

Antibody	Reactivity	Staining Pattern	Comment
CK-PAN	Positive	Cytoplasmic	All tumor cells positive in all cases
Vimentin	Positive	Cytoplasmic	Nearly all tumor cells, much stronger than adenoid cystic carcinoma
p63	Positive	Nuclear	Strong and diffuse, localized to peripheral tumor cells adjacent to connective tissue stroma
S100	Positive	Nuclear & cytoplasmic	Nearly 100% of all tumor cells in all cases, stronger expression than adenoid cystic carcinoma
CEA-M	Positive	Cytoplasmic	~ 55% of tumor cells positive
CK7	Positive	Cytoplasmic	
CK5/6	Positive	Cytoplasmic	
EMA	Positive	Cytoplasmic	Most tumor cells reactive
CD117	Positive	Cytoplasmic	Most tumors will show variably immunoreactive
Actin-sm	Positive	Cytoplasmic	~ 10-15% of tumor cells positive (abluminal)
Calponin	Positive	Cytoplasmic	
Actin-HHF-35	Positive	Cytoplasmic	Variable (abluminal)
Myosin	Positive	Cytoplasmic	
Maps in	Positive	Cytoplasmic	
GFAP	Positive	Cytoplasmic	~ 10-15% of tumor cells show faint, focal, or weak reactivity in luminal cells
Bcl-2	Positive	Nuclear	All tumor cells positive
Ki-67	Positive	Nuclear	Low proliferation index (< 6%)
p53	Positive	Nuclear	Only in rare isolated cells
MCM2	Positive	Nuclear	Usually < 9%
Galectin-3	Positive	Cytoplasmic	Variably positive, different from nuclear reaction in adenoid cystic carcinoma
E-cadherin	Positive	Cell membrane	
Nestin	Positive	Cytoplasmic	Focal, abluminal cells will be positive
Cyclin-D1	Negative		Different from nuclear reaction in adenoid cystic carcinoma

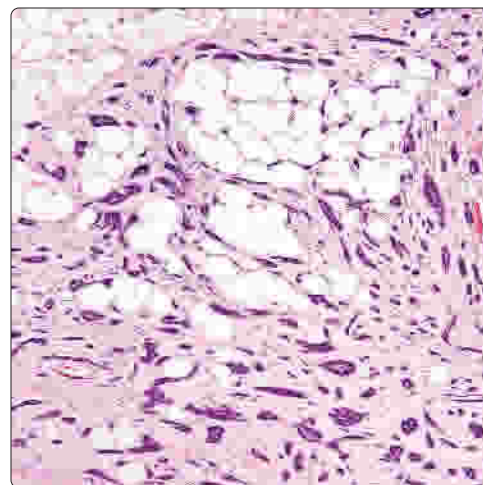
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Multiple Tumor Patterns


(Left) The low-power appearance of these tumors is that of multiple different patterns, hence the name polymorphous. A swirling or eye of the storm pattern is quite characteristic for this neoplasm. **(Right)** Single cells and small strands of neoplastic cells are extending into the adjacent adipose connective tissue. There is a background of bluish-gray matrix. The cells are small and bland, even at this low magnification.

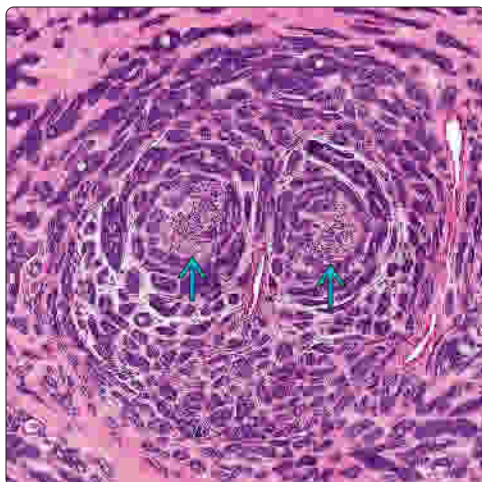


Fat Infiltration

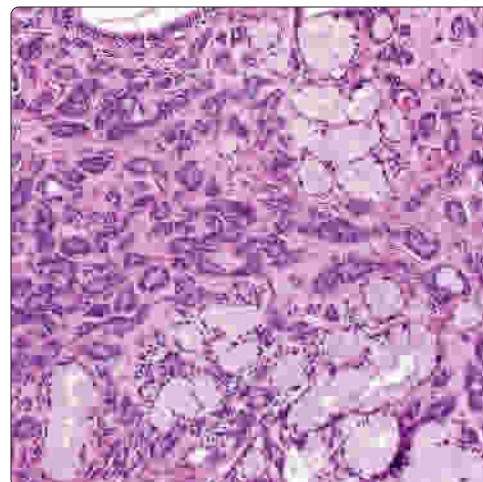


Perineural Invasion



(Left) An intermediate power demonstrates 2 nerves  creating a nidus with concentrically arranged tumor cells in thin strands. This targetoid appearance around a peripheral nerve is quite characteristic for PLGA. **(Right)** Native minor mucous glands are surrounded, but not destroyed, by the neoplastic infiltrate. This encasement or entombment is quite characteristic of PLGA. This does not represent mucinous differentiation in the neoplastic cells.

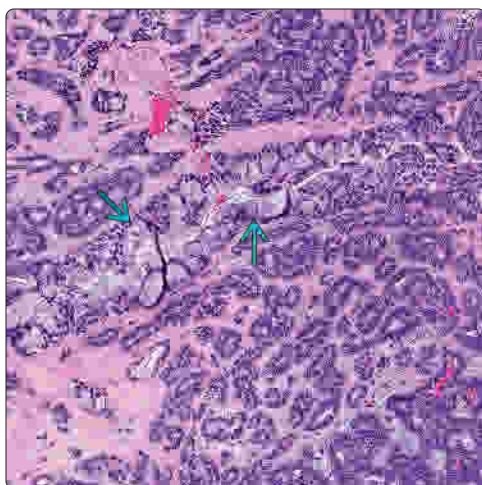


Minor Salivary Gland Entombment

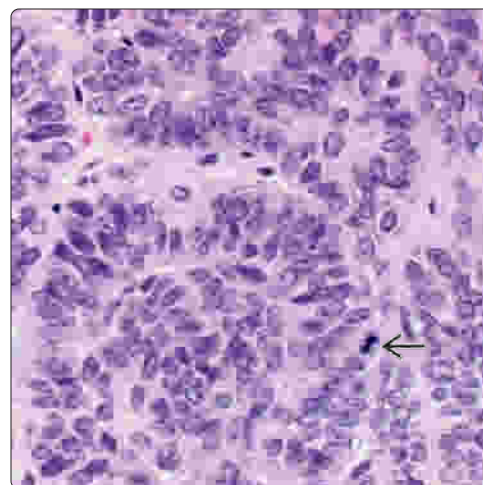


Gland and Duct Entrapment

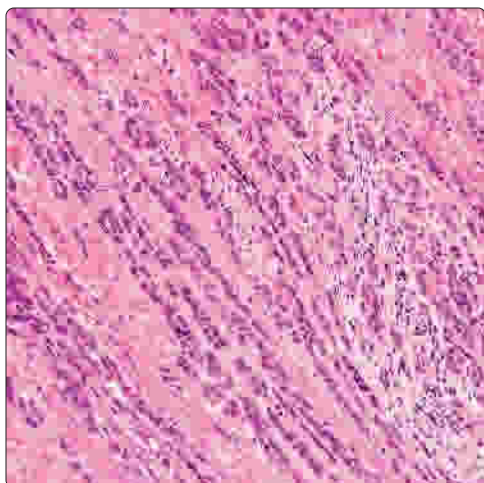
(Left) A minor salivary gland and duct are present in the center of this field , entirely surrounded, although not destroyed by the neoplasm. There is densely collagenized stroma as well as areas of bluish myxoid stroma. **(Right)** The neoplastic cells of PLGA are usually bland cytologically, showing round to oval nuclei with delicate, open to vesicular nuclear chromatin distribution. Nucleoli are small. There is a single mitosis .



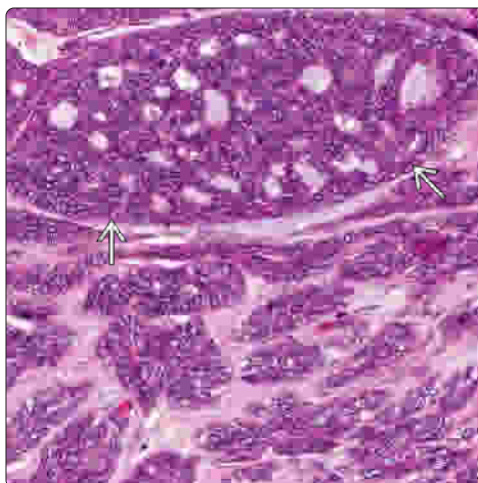
Delicate Chromatin and Mitosis



Single File Infiltration

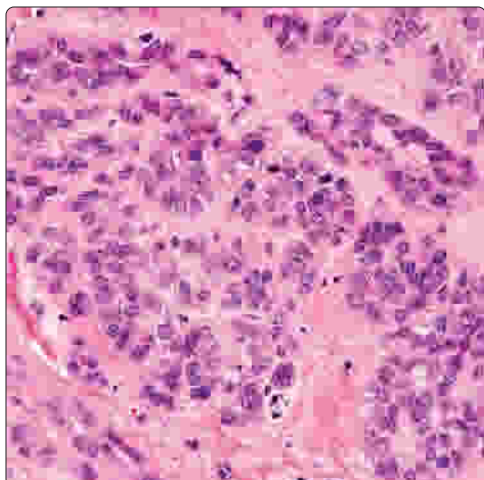


Uncommon Cribriform Pattern

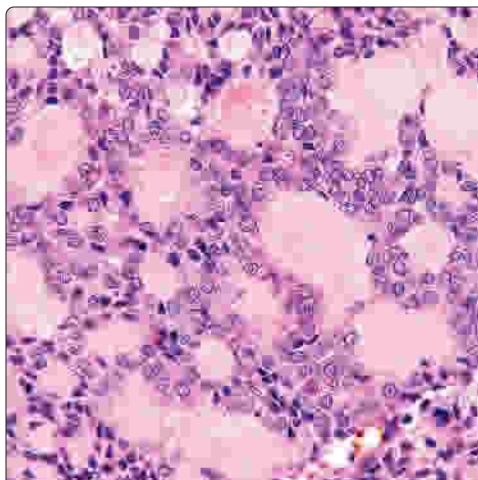


(Left) The tumor cells are frequently arranged in a single file (Indian-filing) pattern, reminiscent of infiltrating lobular breast carcinoma (hence the previous name). Heavy fibrosis separates the tumor cells. (Right) A cribriform pattern of growth [box], along with a tubular/trabecular pattern, is observed in PLGA. The patterns are often juxtaposed to one another, as in this case, although blending is also common.

Cytologically Bland Neoplastic Cells

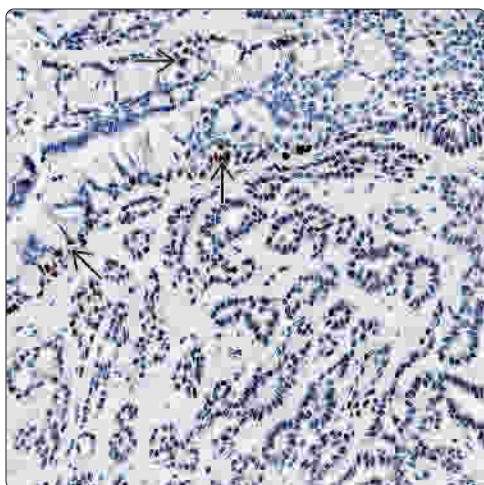


Basement Membrane-Type Material

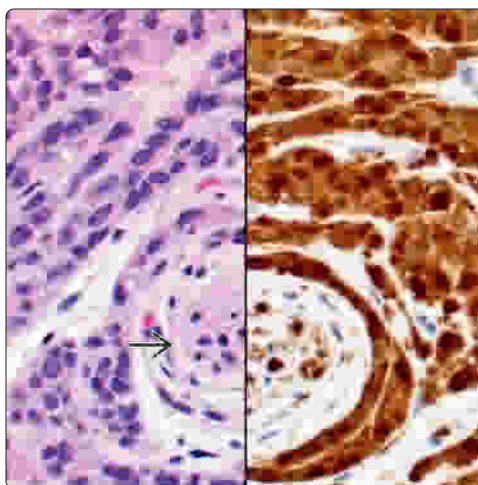


(Left) The neoplastic cells are cytologically bland, arranged in vague nested or glandular patterns. There is open, delicate, vesicular nuclear chromatin. Nucleoli are small and inconspicuous. (Right) A cribriform architectural arrangement of the tumor cells around reduplicated basement membrane material mimics the appearance of adenoid cystic carcinoma, although the cytologic features are different. The chromatin is delicate and even rather than heavy and coarse.

p63(+) Reaction



S100 Protein Reaction



(Left) The neoplastic cells are interpreted to be epithelial and myoepithelial, which is why they will show strong and diffuse immunoreactivity with p63, S100 protein, keratin, and CEA. In this case, the native duct shows residual p63 immunoreactive basal/myoepithelial cells [box]. (Right) The neoplastic cells usually show a strong and diffuse nuclear and cytoplasmic reaction with S100 protein (right). There is a nerve in the center [box], also highlighted by the S100 protein.

Cribriform Adenocarcinoma of Minor Salivary Glands

KEY FACTS

TERMINOLOGY

- Cribriform adenocarcinoma of minor salivary glands (CAMSG)
- Minor salivary gland adenocarcinoma showing cribriform architecture, open nuclear chromatin, and paradoxical propensity for metastatic disease, considered variant of polymorphous low-grade adenocarcinoma (PLGA)

CLINICAL ISSUES

- Range: 21-85 years (mean: 57 years)
- Vast majority affect tongue (usually base)
- 30% of patients have cervical lymph node metastases at time of diagnosis
- Managed with wide excision, often accompanied by neck lymph node dissection

MACROSCOPIC

- Unencapsulated, white-tan to gray, hard consistency

MICROSCOPIC

- Invasive periphery (muscle, bone, vessels, nerves)
- Solid, cribriform to microcribriform structures
- Fibrous septa separate solid mass into irregularly shaped and variably sized nodules
- Central comedonecrosis
- Mucinous-spindle cell myofibroblastic stromal septa (~ 1/3 of cases)
- Nuclei are ovoid to irregular, with pale, optically clear to ground-glass vesicular chromatin
- Nucleoli are small and often peripherally located


ANCILLARY TESTS

- **Positive:** AE1/AE3, CAM5.2, CK7, CK8, CK18, p63, S100 protein, SMA, calponin
- *PRKD* fusions or rearrangements

TOP DIFFERENTIAL DIAGNOSES

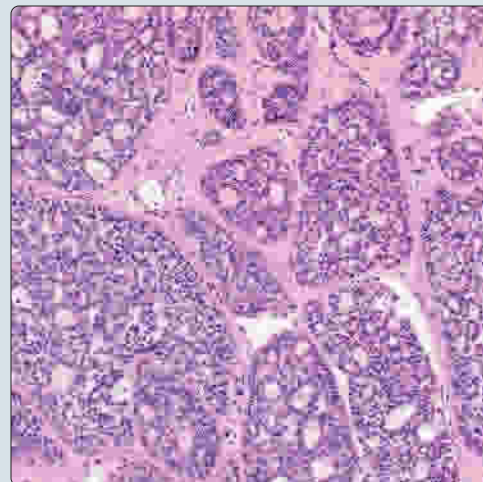
- Metastatic thyroid papillary carcinoma; PLGA (variant)

Cribriform Pattern of Growth

(Left) An intact surface epithelium is seen above the neoplastic proliferation. An area of comedonecrosis  is seen within the center of large cribriform nest. (Right) There are bands of fibrosis that separate the tumor into islands. The tumor nests show a cribriform pattern, with eosinophilic material present in the center (a mimic of colloid).

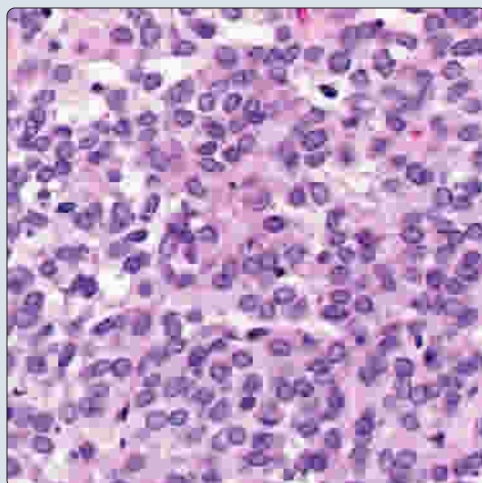


Glandular Architecture With Fibrous Bands

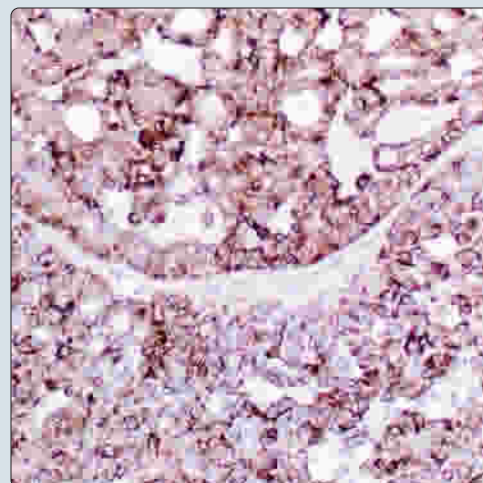


Delicate, Open Nuclear Chromatin

(Left) The nuclei are round to oval, showing focal nuclear grooves and folds. The nuclear chromatin is delicate, even, and vesicular to open. Small nucleoli are present. These mimic thyroid papillary carcinoma. (Right) The neoplastic cells are strongly and diffusely reactive with CK7, along with S100 protein and p16 (not shown).



CK7 Immunoreactivity



TERMINOLOGY

Abbreviations

- Cribriform adenocarcinoma of minor salivary glands (CAMSG)

Synonyms

- Cribriform adenocarcinoma of tongue (CAT)
- Polymorphous adenocarcinoma (WHO term)

Definitions

- Minor salivary gland adenocarcinoma showing cribriform architecture, open nuclear chromatin, and paradoxical propensity for metastatic disease, considered variant of polymorphous low-grade adenocarcinoma (PLGA)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare
- Age
 - Range: 21-85 years (mean: 57 years)
- Sex
 - Male:female = 1:2

Site

- Vast majority affect tongue (usually base)
- Soft palate, retromolar buccal mucosa, tonsil, lip

Presentation

- Mass
- 30% of patients have cervical lymph node metastases at time of diagnosis

Treatment

- Surgical approaches
 - Wide excision, often with neck lymph node dissection
- Radiation
 - ~ 50% receive radiation

Prognosis

- Generally good, in spite of developing metastatic disease
 - Of patients with follow-up, all are alive without additional metastases (mean: 4.3 years)

MACROSCOPIC

General Features

- Unencapsulated, white-tan to gray, hard consistency, generally lacking necrosis and hemorrhage
- Mean: 2.1 cm

MICROSCOPIC

Histologic Features

- Covered by intact, uninvolved squamous epithelium (lacking ulceration or dysplasia)
- Invasive periphery
 - Skeletal muscle, bone, or nerves
 - Lymphovascular invasion in ~ 30%
- Solid, cribriform to microcribriform structures
- Fibrous septa separate solid mass into irregularly shaped and variably sized nodules

- Central comedonecrosis
- Stroma-to-epithelial clefting creates glomeruloid appearance
- Vague peripheral palisade (especially at cleft) can be seen
- Tubules interspersed (similar size) with single cell layer
- Mucinous spindle cell myofibroblastic stromal septa (~ 1/3 of cases)
- Monotonous neoplastic cells lacking overt pleomorphism
- Nuclei are ovoid to irregular, with pale, optically clear to ground-glass vesicular chromatin
 - Morphologically similar to thyroid papillary carcinoma nuclei
- Nucleoli are small and often peripherally located
- Mitoses inconspicuous; clear cell change (central tumor) can be seen; rare, psammoma bodies

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** AE1/AE3, CAM5.2, CK7, CK8, CK18, S100 protein, SMA, calponin
- Variable: Galectin-3, CK19, HBME-1, CD117, p16 (5-60% of cells); cyclin-D1, p53
- Variable: p63, CK14, and CK5/6 tend to stain periphery of nodules
- **Negative:** EMA, p40, HER2/neu, ER, PR, TTF-1, thyroglobulin

Genetic Testing

- *PRKD* fusions or rearrangements
 - *ARID1A-PRKD1*; *DDX3X-PRKD1* fusions
 - *PRKD1*, *PRKD2*, and *PRKD3* rearrangements or fusions

DIFFERENTIAL DIAGNOSIS

Polymorphous Low-Grade Adenocarcinoma

- Wide architectural diversity, but targetoid and streaming single cell pattern is classic
- Perineural invasion (target-like)
- Cellular monotony is also seen, but the nuclei tend not to be cleared
- Background stroma is myxoid and gray-blue

Metastatic Thyroid Papillary Carcinoma

- Solid to cribriform pattern is uncommon
- Presence of colloid (often scalloped) and well-developed psammoma bodies
- **Positive** reactions with TTF-1, pax-8, and thyroglobulin

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Carcinoma Ex-Pleomorphic Adenoma

KEY FACTS

TERMINOLOGY

- Presence of carcinoma arising from primary (de novo) or recurrent pleomorphic adenoma

CLINICAL ISSUES

- Usually presents in 6th to 8th decades
- Parotid (80%) >> minor salivary glands
- Long clinical history of painless mass with recent rapid enlargement and nerve palsy
- Complete surgical eradication with postoperative radiation
- Local recurrence is common (up to 50%) with metastases (up to 70%)
- Prognostically significant factors include stage, grade, extent of invasion, histologic subtype, tumor size, proportion of carcinoma, high proliferation index, margin status, primary vs. recurrent PA, and perineural invasion

MACROSCOPIC

- Poorly circumscribed and invasive

- Range: Up to 25 cm; mean: ~ 5 cm

MICROSCOPIC

- Epithelial (luminal) or myoepithelial (nonluminal) malignancies comprise carcinoma
- Carcinomatous component includes SDC, adenocarcinoma, NOS, ACC, and MEC most commonly
- Carcinoma shows significant pleomorphism, increased mitoses, necrosis, hemorrhage, and destructive growth
- Separation based on extent of invasion
 - Noninvasive, minimally invasive, invasive

ANCILLARY TESTS

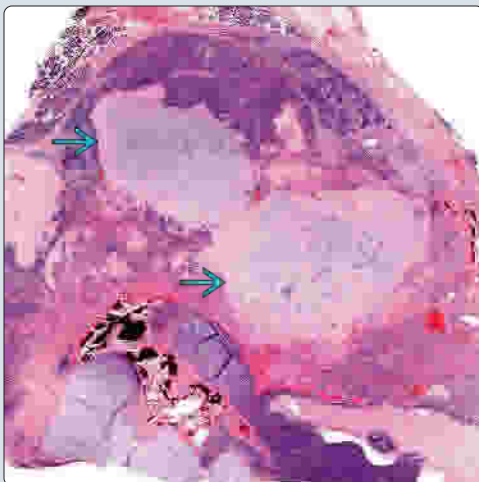
- Increased frequency **in carcinoma areas** with Ki-67, p53, HER2/neu and androgen receptor (in SDC)

TOP DIFFERENTIAL DIAGNOSES

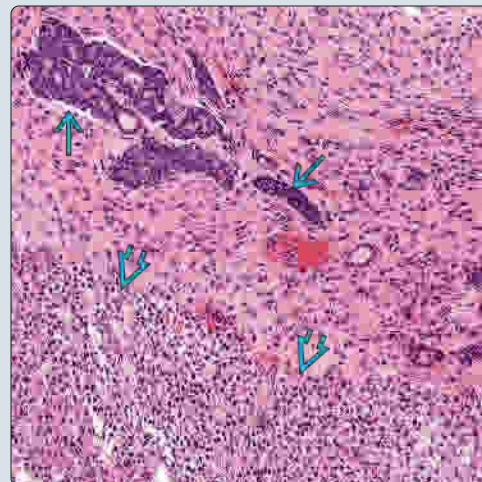
- Pleomorphic adenoma
- Metastatic carcinoma
- Salivary duct carcinoma

Multiple Patterns in Carcinoma Ex-Pleomorphic Adenoma

(Left) The degree of cellularity and architectural variability in this case is characteristic for carcinoma ex-pleomorphic adenoma (CEPA). Note the islands of cartilaginous matrix. (Right) The carcinomatous elements of a CEPA can be a variety of different tumor types, both within and between tumors. In this case, the carcinoma is an adenoid cystic carcinoma (ACC), blending with areas of pleomorphic adenoma (PA).

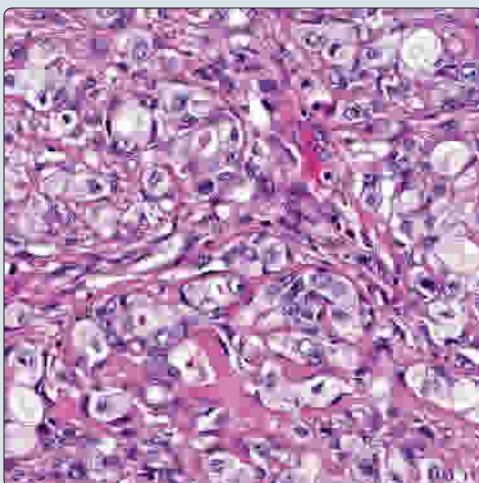


Adenoid Cystic Carcinoma Within Pleomorphic Adenoma at Zone of Transition

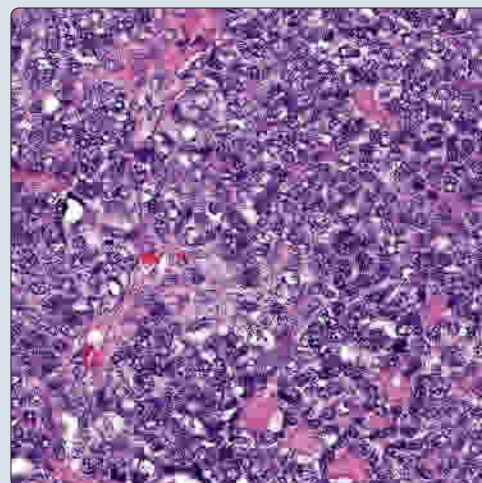


Pleomorphism Within Carcinoma

(Left) In many tumors, the malignant transformation begins with the luminal duct-like areas, filling in along the myoepithelial-lined spaces. This feature can be highlighted with immunohistochemistry for myoepithelial or basal markers. (Right) Undifferentiated or poorly differentiated carcinomas can be seen within CEPA. There is a very high nuclear:cytoplasmic ratio. There is no residual PA in this field.



Undifferentiated Carcinoma Component



TERMINOLOGY

Abbreviations

- Carcinoma ex-pleomorphic adenoma (CEPA or CXPA)
- Pleomorphic adenoma (PA)

Synonyms

- Carcinoma ex-benign mixed tumor
- Malignant mixed tumor
- Carcinoma arising in benign mixed tumor
- Carcinoma arising in PA

Definitions

- Presence of carcinoma arising from primary (de novo) or recurrent pleomorphic adenoma
 - Requires concurrent pleomorphic adenoma histologically or history of pleomorphic adenoma at same site
 - Carcinoma can be any epithelial neoplasm
 - e.g., salivary duct carcinoma (SDC), adenocarcinoma, not otherwise specified (NOS), adenoid cystic carcinoma (ACC), mucoepidermoid carcinoma (MEC), myoepithelial carcinoma, polymorphous low-grade adenocarcinoma (PLGA), epithelial-myoepithelial carcinoma (EMC)
- Diagnosis is category of diagnoses, including in situ and low-grade (indolent) tumors and high-grade neoplasms

ETIOLOGY/PATHOGENESIS

Development

- There is malignant transformation of epithelial component
 - Transition helps substantiate continuum
- Progressive loss of heterozygosity at chromosomal arms 8q, then 12q, and then 17p
- Quantitative promoter methylation shows significant difference in various tumor suppressor genes (TSGs) between PA and CEPA

CLINICAL ISSUES

Epidemiology

- Incidence
 - Accounts for ~ 4% of all salivary tumors
 - 12% of all salivary malignancies
 - 7-10% of all pleomorphic adenomas
- Age
 - Usually in 6th to 8th decades
 - ~ 10-12 years older than age at presentation of PA
 - Exceptional in children
- Sex
 - Equal gender distribution (taking institution bias and reporting into consideration)
- Ethnicity
 - Prevalence differences between different countries
 - United Kingdom: 25% of parotid malignancies vs. Switzerland: 14% vs. USA: 12%, respectively

Site

- Major salivary glands most often (80%)
 - Parotid (80%) > submandibular (18%) > > sublingual gland (< 2%)

- May be due to large tumor size and increased recurrence rate for major gland location
- Minor glands (20%)
 - Palate > > nasopharynx > nasal cavity > > larynx
 - On average, smaller than major salivary gland tumors

Presentation

- Long clinical history of pleomorphic adenoma
 - Greater length of time with tumor, higher risk of malignant transformation
 - 5 years: 1.6%; 15 years: 9.6%
 - Symptoms/mass present for up to 44 years
 - Mean duration: 9 years
 - Need to have well-documented previous tumor in same anatomic site if there is no histologic evidence of benign PA
 - Some tumors are slow-growing and asymptomatic, so long history of mass by itself is insufficient
- May have had multiple surgeries
 - ~ 20% have had previous surgery
- Usually, recent rapid enlargement
- Nerve palsies are common (30-40%)
- Majority are painless
- Rare: Skin ulceration, skin fixation, soft tissue attachment, bone invasion, dysphagia

Treatment

- Surgical approaches
 - Complete surgical eradication
 - Facial nerve must be sacrificed in most cases
 - Lymph node dissection often required (~ 20%)
 - Some recommend neck dissection for all major gland tumors
 - Lymph node dissection may not be necessary for low-grade carcinomas or those with limited invasion
- Radiation
 - Majority receive postoperative radiation therapy
 - Especially used for widely invasive &/or high-grade tumors
 - May be useful in controlling local disease

Prognosis

- Local recurrence can be seen (range: 25-50%)
 - Majority are seen within 5 years of diagnosis
 - Many patients experience more than 1 recurrence
 - Recurrence rates tend to be lower for minor salivary gland primaries
 - Higher percentage of patients die with disease if they have local recurrence
- Local or distant metastases are common (range: 50-70%)
 - Local lymph node metastases: Up to 25%
 - May be higher if there was previous surgery
 - Distant sites: Lung, bone (spine), liver, brain, skin
 - Most common in patients with local recurrence
- Poor overall survival
 - Majority die of disease (60%)
 - 5-year survival (30%)
 - CEPA has worse outcome than same carcinoma type not arising in association with PA
- Prognostically significant factors (order of importance)
 - **Stage**

Carcinoma Ex-Pleomorphic Adenoma

- > 2 cervical lymph nodes affected by metastatic disease
- **Grade**
 - Low grade: Tend not to die of tumor
 - High grade: Majority die from tumor
- **Extent of invasion**
 - Noninvasive (encapsulated): Excellent long-term outcome (identical to conventional PA)
 - Minimally invasive tumors (≤ 1.5 mm): Good outcome (75-85% at 5 years)
 - Widely invasive (> 1.5 mm): Poor outcome (25-65% at 5 years)
 - Other cutoffs are proposed, but not yet widely used or validated (2, 3, 5, 6, 7, 8, or 15 mm)
- **Histologic subtype**
 - Polymorphous low-grade adenocarcinoma (PLGA): 96% 5-year survival
 - Salivary duct carcinoma: 62% 5-year survival
 - Myoepithelial carcinoma: 50% 5-year survival
 - Undifferentiated carcinoma: 30% 5-year survival
- **Large tumor size**
- **Proportion of tumor that is carcinoma**
- **High proliferation index**
- **Margin status**
 - Positive margins predict higher recurrence rate and higher death rate from tumor
- **Primary vs. recurrent PA**
 - CEPA associated with recurrent PA worse than that for CEPA associated with primary PA
- **Perineural invasion**

IMAGING

Radiographic Findings

- Location, extent, and lymph node status can be established
- Areas of benign PA may be identified
 - Areas of calcification more common in PA
- Ill-defined margin or loss of sharp margin is often clue to malignancy
- Low T2 MR signal in solid mass is worrisome for malignancy
- Perineural spread along CN VII in temporal bone
 - Facial nerve plane separating superficial and deep lobes of parotid may be lost

MACROSCOPIC

General Features

- Circumscribed and encapsulated tumors may be seen
- Most tumors are poorly circumscribed with invasion easily identified
 - Area of circumscription may represent residual PA
 - Area of scarring may also represent residual PA
- Necrosis and hemorrhage may be present
- Benign areas: Translucent gray-blue
- Carcinoma areas: Firm, white, tan or gray

Sections to Be Submitted

- Must submit areas of transition between possible benign and malignant zones
 - Must submit from periphery to assess invasion

Size

- Range: Up to 25 cm; mean: ~ 5 cm
- Average size: ~ 2x that of PA

MICROSCOPIC

Histologic Features

- Epithelial (luminal) or myoepithelial (nonluminal) malignancies comprise carcinoma
- Carcinomatous component may be part of specific tumor type
 - SDC; adenocarcinoma, NOS; ACC; MEC; myoepithelial carcinoma; PLGA; EMC
 - Epithelial and myoepithelial components together
 - Epithelial component only
 - Myoepithelial component only
 - SDC is most common carcinoma type
 - Carcinoma shows
 - Significant pleomorphism (enlarged pleomorphic cells with hyperchromatic nuclei, prominent nucleoli)
 - Increased mitotic figures
 - Areas of necrosis
 - Areas of hemorrhage
 - Destructive growth
- Relative proportions of carcinoma and adenoma vary widely
 - Malignant and benign components juxtaposed
 - Malignant and benign blended
 - Sclerotic nodule in malignant tumor suggests residual PA
 - Multifocal, distinct, and separate malignant nodules
 - Carcinoma ranges from focal to diffuse
 - In majority of cases, carcinoma represents > 50% of tumor volume
 - Malignant cells replace inner duct layer, leaving peripheral myoepithelial layer intact
 - Extensive sampling may be required to document PA
 - Carcinoma frequently overgrows and replaces benign areas
 - In rare cases, clinical history of tumor at same site may be only PA documentation
- Separated into low and high grade
 - Based on degree of pleomorphism, necrosis, increased mitoses
- Concurrent PA is very frequently extensively hyalinized (fibrotic, scarred)
- Separation based on extent of invasion, although exact distances and measurement techniques are being reevaluated
 - **Noninvasive** (encapsulated) carcinoma without evidence of capsular invasion
 - **Minimally invasive:** Distance from capsule to distant extent of tumor is ≤ 1.5 mm
 - **Invasive:** Distance from capsule to distant extent of tumor is > 1.5 mm
 - Difficulties in determining invasion distance; different cutoffs of 2, 3, 5, 6, 7, 8, or 15 mm applied
 - Mean invasion: 24 mm
- Destructive soft tissue (fat, skeletal muscle) invasion is common
- Widely invasive tumors tend to be myoepithelial carcinomas

- Perineural and vascular invasion are routinely seen
 - Must be certain is atypical epithelium in vascular spaces
- Poorly differentiated high-grade adenocarcinoma that is difficult to classify raises possibility of CEPA
- When metastatic, only carcinomatous component has been identified

Margins

- Negative margins are difficult to achieve due to bosselation or nodularity of tumor

Carcinosarcoma

- **True** malignant mixed tumor
- Pleomorphic adenoma with carcinoma and sarcoma concurrently present
- Much more aggressive than CEPA
- Most common elements are chondrosarcoma and carcinoma
 - Osteosarcoma, fibrosarcoma, and rhabdomyosarcoma are rare

Benign Metastasizing Pleomorphic Adenoma

- Benign pleomorphic adenoma in distant site
 - Lung, liver, kidney, and lymph nodes
- Believed to be iatrogenic in patient with history of multiple recurrences and multiple surgeries for PA
- Benign epithelial elements within vessels adjacent to pleomorphic adenoma
- Histologically benign without any cytologic atypia in distant foci
- Most follow similar outcome as PA, but adverse behavior may occur

ANCILLARY TESTS

Cytology

- Marked variation in type and grade of carcinoma, coupled with unknown benign and malignant proportions, make FNA interpretation difficult
- Adequate sampling is critical (to avoid false-negative)
 - Must be extensively sampled to exclude malignant transformation
 - Large lesions, recurrent lesions, or tumors of long duration
 - Low sensitivity due to sampling error
 - Grade of malignant tumor may help with separation
 - Highly malignant epithelial cells (SDC) are relatively straightforward (especially with cell block material)
 - Low-grade carcinoma (MEC, adenocarcinoma, NOS) may be more difficult to separate
- Cellular smears, with epithelial predominant population
- May show 2 distinct patterns
 - Unequivocal groups and single malignant cells admixed with benign epithelial and stromal components of PA
 - Groups, sheets, papillary structures, cribriform pattern
 - Large cells, pleomorphic nuclei, prominent nucleoli, increased mitotic figures, necrosis
 - Variably pleomorphic cells, without clear-cut malignant criteria, with mixture of epithelial and stromal components of PA

Immunohistochemistry

- Carcinomas separated into

- Epithelial only (majority): AE1/AE3, EMA, CK7, CK8, CK19 (+)
- Epithelial and myoepithelial (~ 25%)
 - AE1/AE3, EMA, CK7, CK8, CK19: Ductal
 - p63, CK5/6, α -SMA, CK14: Myoepithelial
- S100 protein, GFAP: Helps confirm PA component
- p63 may highlight myoepithelial/basal cell compartment for in situ/intratubular determination
- Increased frequency in **carcinoma areas** with
 - Ki-67 (MIB-1): > 35% in carcinoma areas
 - p53 (overexpressed in carcinoma vs. benign PA)
 - Strong overexpression and amplification of HER2/neu (c-erbB-2)
 - Also associated with and present in high tumor grade
 - Androgen receptor expressed in SDC, highlights area of carcinoma transformation (**negative** in PA)
 - Vascular endothelial growth factor (VEGF), glucose transporter 1 (GLUT1), epidermal growth factor receptor (EGFR)
 - Minichromosome maintenance protein-2 (MCM2) (higher labeling index [> 20%] than PA [~ 7%])
- Laminin, collagen IV, tenascin, and fibronectin are variably expressed based on type and degree of invasion present
- Neural cell adhesion molecule (NCAM) is absent or weak in carcinoma component

Flow Cytometry

- Aneuploid population possible in high-grade CEPA
- Ploidy does not predict tumor behavior

Genetic Testing

- Rearrangements/amplifications of *PLAG1* (pleomorphic adenoma gene 1) or *HMG2* (detected by FISH) may help confirm transformation vs. de novo development
- Multiple structural, numeric, and chromosome deletions reported (6q, 8q, 12q)
 - Alterations at 12q13-15 (amplification of *HMGIC* and *MDM2* genes)
- p53 (17p13): Point mutations or loss (detected by gene sequencing), often results in p53 protein overexpression
- p16: Decreased immunohistochemical expression in carcinoma (but may not equate to specific molecular alteration)
- Progressive loss of heterozygosity (LOH) identified at chromosome 8q, 12q, and then 17p
 - Specifically: 8q11.23-q12, 12q23-qter, 17p13, 17p11
 - 8q22.1-q24.1 involves *MYC*, with consequent overexpression
 - Frequently in all 3 chromosomal arms
 - 17p may correlate with stage and proliferation

DIFFERENTIAL DIAGNOSIS

Pleomorphic Adenoma

- Completely encapsulated, although bosselated and nodular periphery
- Recurrent tumors are frequently multinodular and multifocal
- Frank anaplasia is absent
- Chondroid material usually identified
- In tumors with extensive sclerosis/hyalinization, additional sampling is recommended to exclude carcinoma

- PAs with high mitotic index are more likely to transform to carcinoma
- Degeneration in PA may have hemorrhage, necrosis, inflammation, and squamous metaplasia
- PA must be identified in CEPA in order to qualify for designation

Metastatic Carcinoma

- Tends to be multifocal
- Shows distinct morphology within background of pleomorphic adenoma
- Lymphovascular emboli are easily identified
- Clinical history is frequently known

Salivary Duct Carcinoma

- High-grade malignancy, showing apocrine phenotype, nearly always androgen receptor (+)
- Most common carcinoma of CEPA, so important to examine many sections to document PA
 - Prognosis for primary and transformed SDC is uniformly bad, but overall worse when identified in CEPA

REPORTING

Key Elements to Report

- Stage, including tumor size and lymph node status
- Histologic subtypes most prognostically significant: SDC, myoepithelial carcinoma
- Degree of differentiation (tumor grade)
- Must report extent of invasion
 - In situ, intracapsular, noninvasive
 - Widely invasive (no matter which distance has been applied)
- Perineural invasion and margin status

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Erythematous and Shiny Parotid Gland Tumor Mass

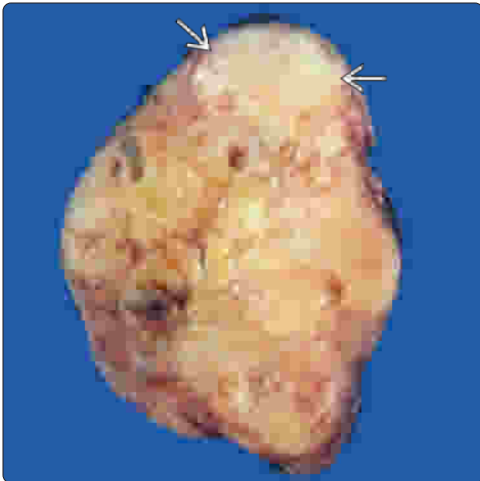


CT of Carcinoma Ex-Pleomorphic Adenoma Showing Calcifications

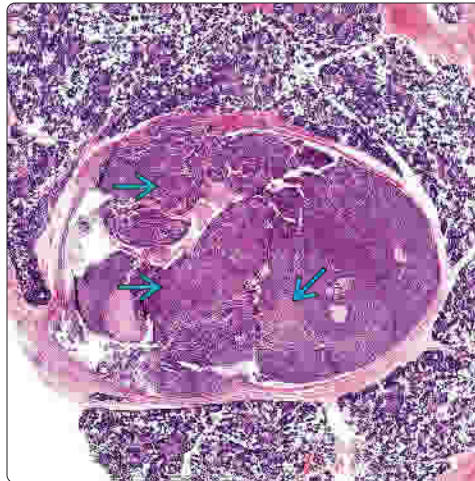


(Left) This retroauricular tumor shows remarkable skin erythema. Ulceration has not yet developed but is likely to develop if left unmanaged. The patient had a history of pleomorphic adenoma. (Right) A mass in the superficial lobe of the parotid gland shows focal osseous metaplasia [B]. Areas of calcification are common in PA. However, there is cystic change and destructive growth, a feature of CEPA (salivary duct carcinoma in this case).

Gross Photograph of Carcinoma Ex-Pleomorphic Adenoma

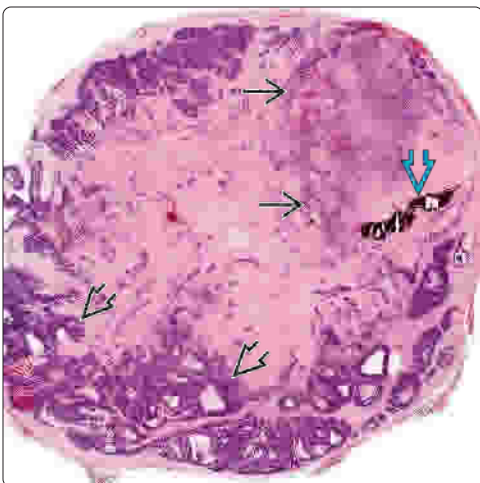


Encapsulated Carcinoma Ex-Pleomorphic Adenoma (Noninvasive)

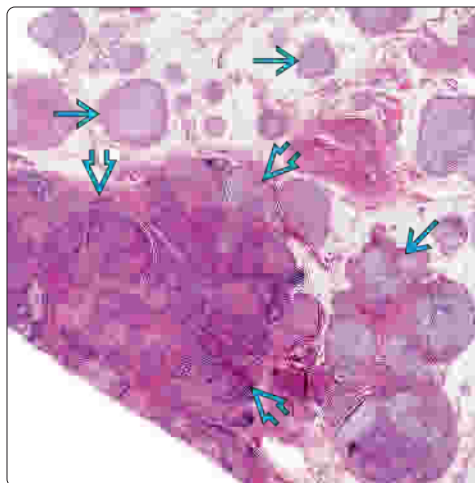


(Left) The neoplasm shows a very fleshy appearance with areas of yellow degeneration, focal cystic change, and hemorrhage. Areas of pale-shiny residual pleomorphic adenoma are noted [B]. It is not uncommon to be able to detect areas of residual pleomorphic adenoma during gross examination. (Right) This is an example of encapsulated CEPA. There is a capsule that shows no invasion. The PA is quite cellular, showing isolated [B], multifocal areas of carcinoma, which were confirmed at high power.

Glandular Pattern in Carcinoma Ex-Pleomorphic Adenoma



Recurrent Pleomorphic Adenoma With Carcinoma Ex-Pleomorphic Adenoma Development



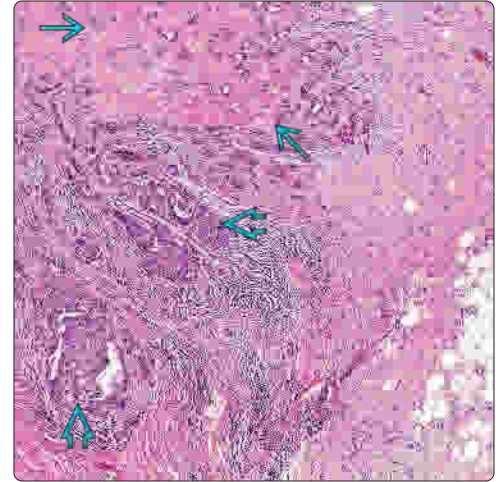
(Left) There is a well-circumscribed tumor, with areas of residual pleomorphic adenoma [B] and calcifications [B] shown here. However, even at low power, the areas of carcinoma [B] are more cellular, with a glandular architecture. (Right) Multiple distinct nodules of PA are noted in the fat [B] that is seen here, a characteristic feature of recurrent PA. However, there is a cellular destructive nodule that shows carcinomatous transformation [B]. Multiple recurrences are common harbingers of malignant transformation.

(Left) This carcinoma has invaded into and through the capsule [E], but does not extend > 1.5 mm. This would be considered a minimally invasive tumor by the current World Health Organization criteria. **(Right)** There is benign, sclerotic PA [E] juxtaposed with areas of carcinoma [E] in this CEPA. There is extension of the tumor in the adjacent fatty tissue. The extent of invasion is an important prognostic indicator, as is tumor grade and type. The tumor is a high-grade adenocarcinoma, not otherwise specified (NOS).

Minimally Invasive Carcinoma Ex-Pleomorphic Adenoma

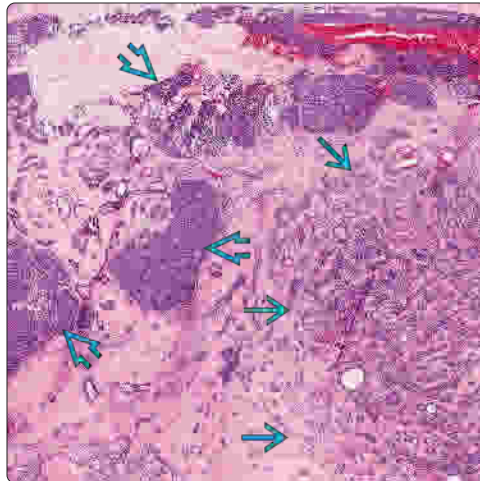


Infiltrative Advancing Edge of Carcinoma

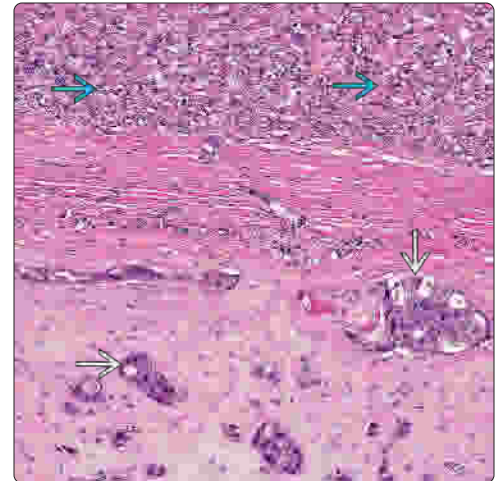


(Left) It is important to document areas of both benign and malignant tumor within the same lesion. The benign PA [E] in this tumor has a different cellularity and degree of cytologic atypia in comparison to the areas of carcinoma [E]. **(Right)** The PA area is cellular, although showing remarkable sclerosis [E]. This fibrosis blends imperceptibly with the areas of frankly pleomorphic carcinoma [E]. Atypia and necrosis are common in carcinoma.

Blending of Benign and Malignant Components

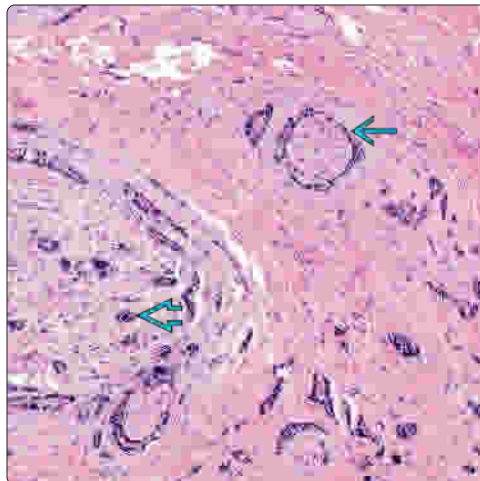


Abrupt Juxtaposition of Benign and Malignant Elements

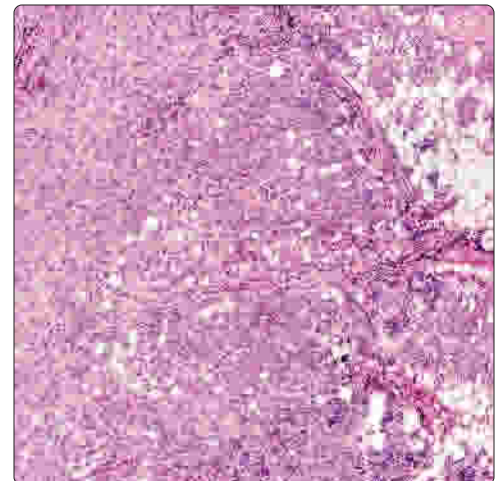


(Left) The neoplastic glandular elements are intimately associated with the nerves, with both perineural [E] and intraneural [E] invasion. Perineural and intravascular invasion are frequent findings in CEPA, and are prognostically significant variables. **(Right)** There is extensive infiltration into the adjacent adipose connective tissue around the parotid gland in this CEPA. No areas of residual PA are seen in this field.

Peri- and Intraneural Invasion



Widely Infiltrative Carcinoma



Fat Invasion by Carcinoma

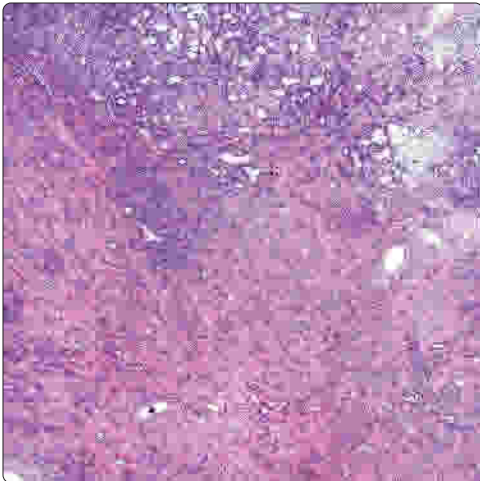


Salivary Duct Carcinoma Arising Within Pleomorphic Adenoma

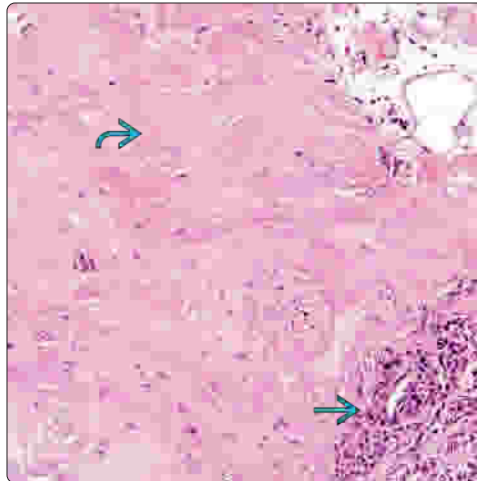


(Left) A variety of different patterns of growth are common for PA, but the degree of cytologic atypia in the carcinomatous areas is beyond the spectrum of a benign neoplasm. This carcinoma has a degree of hyperchromasia that is beyond the benign tumor. Fat invasion is noted. (Right) There is a high-grade adenocarcinoma in this field, changes most consistent with a salivary duct carcinoma type. Note the areas of comedonecrosis [blue arrow] as well as increased fibrosis.

Heavy Intratumoral Sclerosis

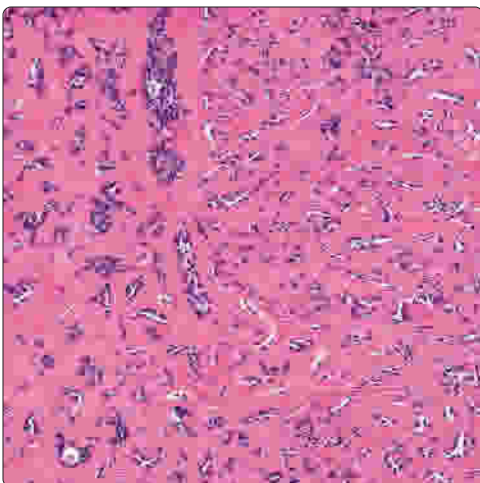


Sclerotic Tumor Fibrosis in Carcinoma Ex-Pleomorphic Adenoma

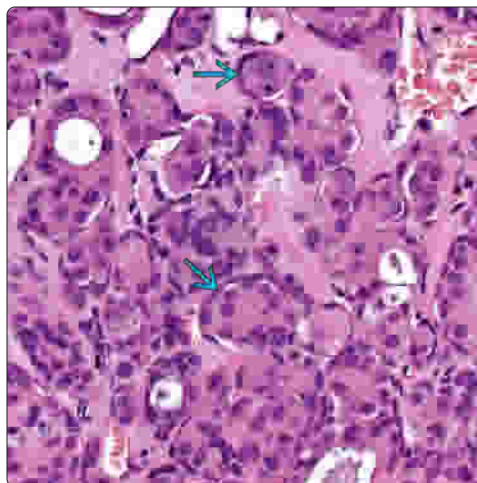


(Left) The presence of increased and heavy intratumoral fibrosis or sclerosis is always worrisome for malignant transformation in a PA. Whenever found, additional or deeper sections are recommended to exclude concurrent carcinoma. (Right) Broad areas of acellular hyalinization [blue arrow], as seen in this PA [blue arrow], may be associated with or herald the development of malignant transformation.

Intratumoral Sclerosis



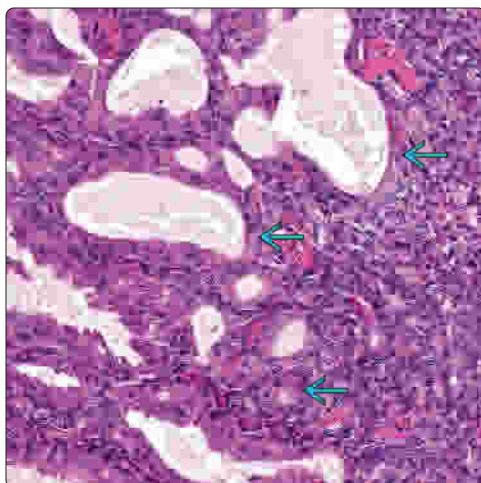
Intratubular Carcinoma



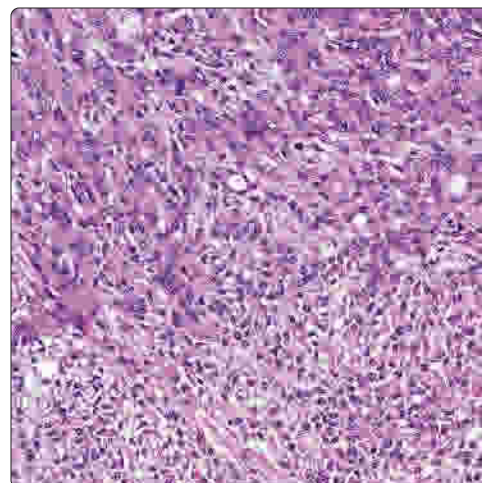
(Left) This degree of stromal hyalinization or scarring in a PA must alert the pathologist to the possibility of a malignant transformation. There is only PA in this field, but carcinoma was noted in additional sections. (Right) There is malignant transformation of the luminal cells, which show marked pleomorphism. However, there is an intact myoepithelial/basal area [blue arrow], showing a DCIS-like pattern (intratubular or intraductal pattern).

(Left) The malignancy in this case was an adenocarcinoma, NOS. It is easy to see the malignant epithelial component [red box] juxtaposed to the areas of benign PA. While salivary duct carcinoma is the most common malignancy, adenocarcinoma, NOS, is still common. **(Right)** The upper part of this image shows a malignant transformation with pleomorphism and increased N:C ratio, while the lower part of the image shows a plasmacytoid population of the benign PA.

Luminal Adenocarcinoma

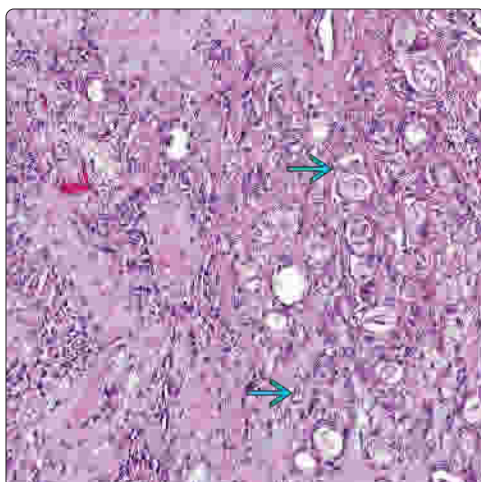


Carcinoma Blended With Pleomorphic Adenoma

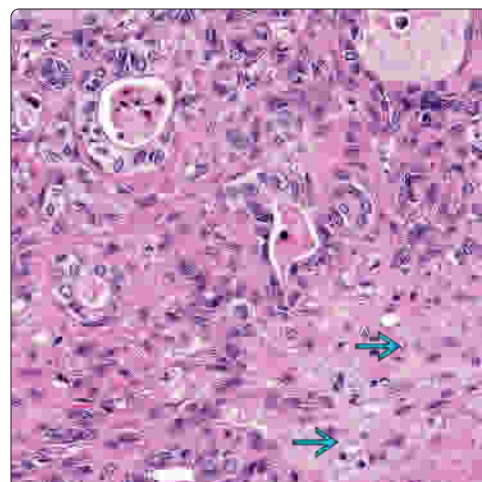


(Left) An intratubular carcinoma is noted [red box] in association with fibrosis, while the benign pleomorphic adenoma (plasmacytoid appearance) is noted in the left field. **(Right)** There is a remarkable degree of cytologic pleomorphism with a sclerotic background stroma. Areas suggestive of residual pleomorphic adenoma [red box] are seen, although limited in this high-power view.

Juxtaposed Carcinoma With Pleomorphic Adenoma

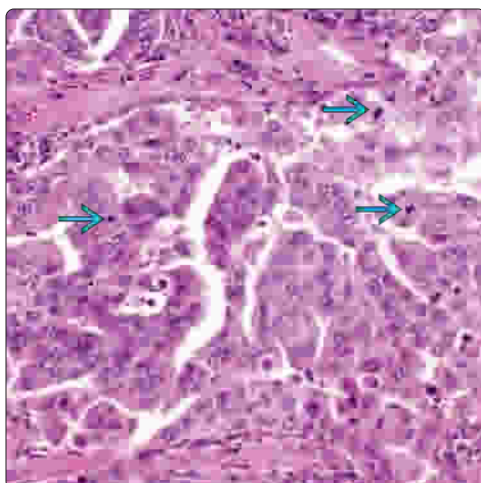


Pleomorphism in Carcinoma

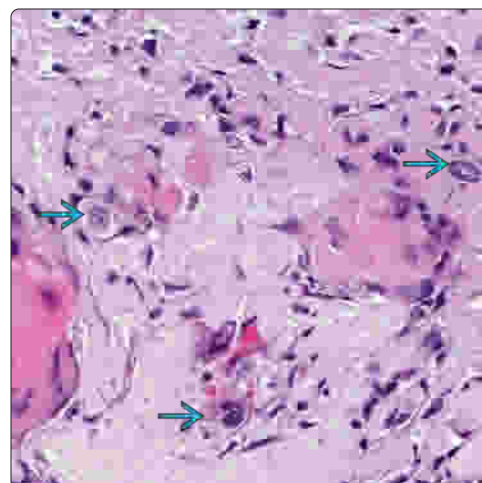


(Left) There is a micropapillary architecture to this part of a salivary duct carcinoma (SDC) arising within a PA. There are also increased mitoses [red box], another helpful feature in identifying areas of carcinoma. **(Right)** Within a densely hyalinized background, islands of metaplastic squamous epithelium are noted. There are many isolated, highly atypical epithelial cells [red box]. These features are quite characteristic of a CEPA.

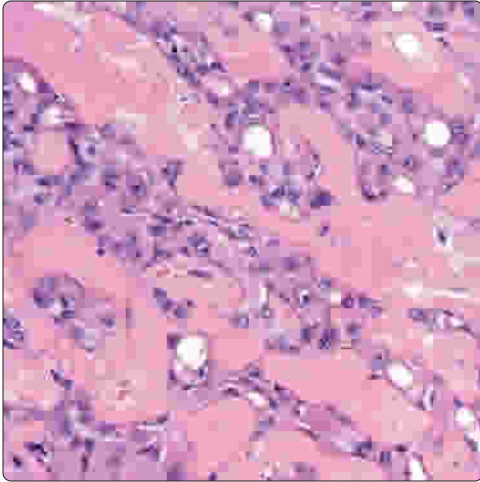
Salivary Duct Carcinoma Arising Within Pleomorphic Adenoma



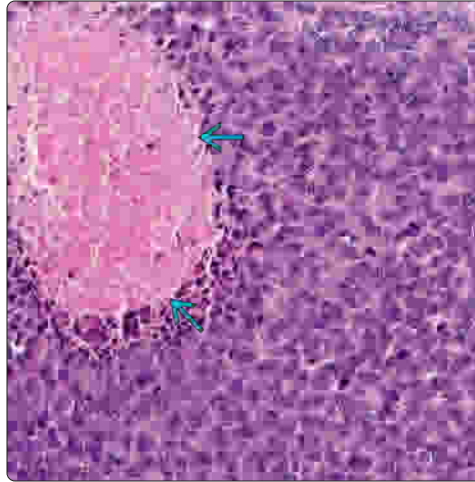
Isolated Malignant Cells in Stroma



Sclerosis and Carcinoma

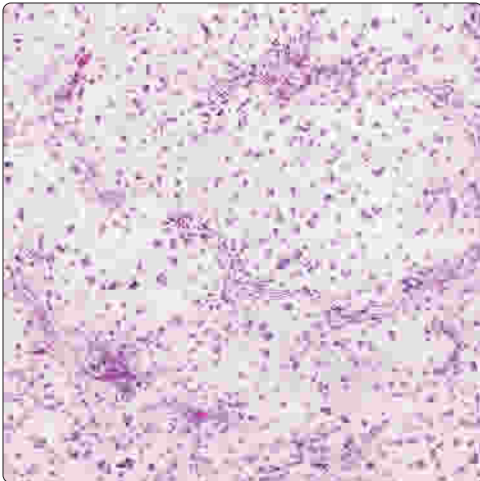


Comedonecrosis in Carcinoma Ex-Pleomorphic Adenoma

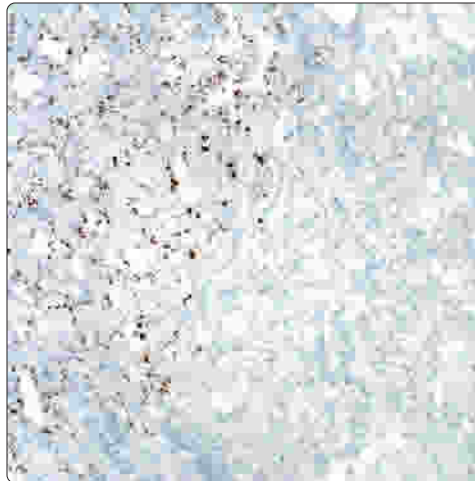


(Left) The malignant cells are noted expanding along the previous tubules or ductules of a PA. Note the very heavy sclerosis separating between the tumor nests. (Right) An area of comedonecrosis is found in this CEPA focus. There is a very high cellularity, associated with increased mitoses. There is a very high nuclear:cytoplasmic ratio and pleomorphism.

Chondrosarcoma in True Malignant Mixed Tumor

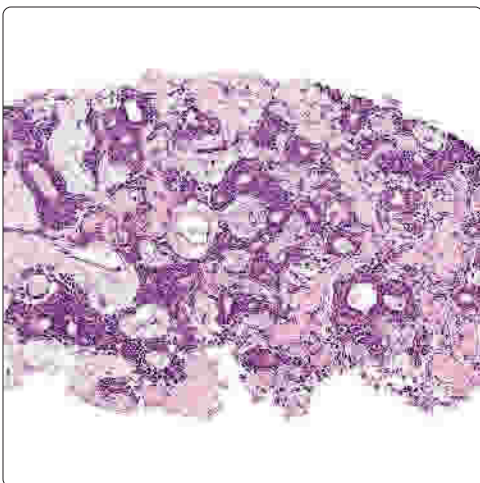


p53 Overexpressed in Carcinoma

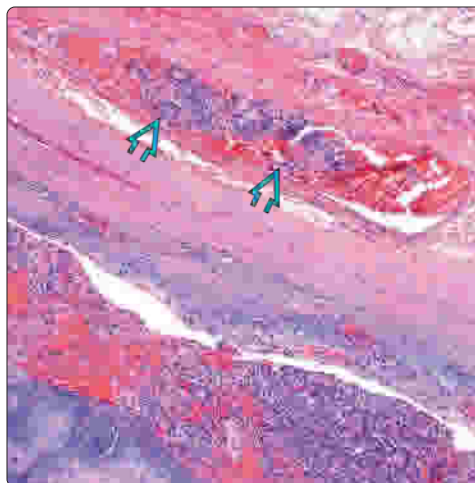


(Left) Uncommonly, there will be a malignant transformation of both epithelial and mesenchymal elements. In this case, the chondrosarcoma is highlighted in a true malignant mixed tumor. Carcinoma was noted elsewhere. (Right) The p53 shows a significantly increased intensity of reaction and the number of cells that are positive in the areas of carcinoma in comparison to areas of PA. This can help in determining a percent of tumor that is malignant.

Benign Metastasizing Pleomorphic Adenoma



Benign Metastasizing Pleomorphic Adenoma



(Left) A core needle biopsy of the kidney shows a benign pleomorphic adenoma. There is an unremarkable epithelial proliferation set in a myxochondroid matrix. The patient had multiple previous surgeries for parotid gland PA; this is an example of benign metastasizing PA. (Right) There is benign PA within a vascular space in this benign metastasizing PA. The tumor thrombus is not composed of malignant or pleomorphic neoplastic cells, but only benign epithelial cells.

Low-Grade Intraductal Carcinoma

KEY FACTS

TERMINOLOGY

- Low-grade intraductal carcinoma (LG-IDC)
- Noninvasive (intraductal) salivary gland neoplasm with intracystic/intraductal growth resembling low-grade ductal carcinoma in situ of breast

CLINICAL ISSUES

- Older (mean: 62 years), but wide range (27-93 years)
- Major glands (parotid vast majority)

MACROSCOPIC

- Well circumscribed, unencapsulated, dominated by multiple cystic spaces

MICROSCOPIC

- Unencapsulated tumor with predominantly cystic structures (enlarged ducts) of variable size
- Intraductal or intracystic epithelial proliferation
- Solid nests/islands, papillae, micropapillae, and loosely formed cribriform structures within cystic spaces

- Multilayered, micropapillary structures and "Roman bridges" frequently seen
- Apocrine snouts may be seen with abundant eosinophilic cytoplasm
- Low, intermediate, or high nuclear grade (dysplasia), but high-grade lesions are uncommon
- Cysts contain eosinophilic debris and macrophages
- Myoepithelial layer surrounds tumor nests or islands

ANCILLARY TESTS

- Luminal cells **positive**: S100 protein, AE1:AE3, CAM5.2, CK7, CK18, CK19, BRST-2, androgen receptor
- Continuous rim of myoepithelial cells **positive**: p63, calponin, CK5/6, CK14, SMA, MSA

TOP DIFFERENTIAL DIAGNOSES

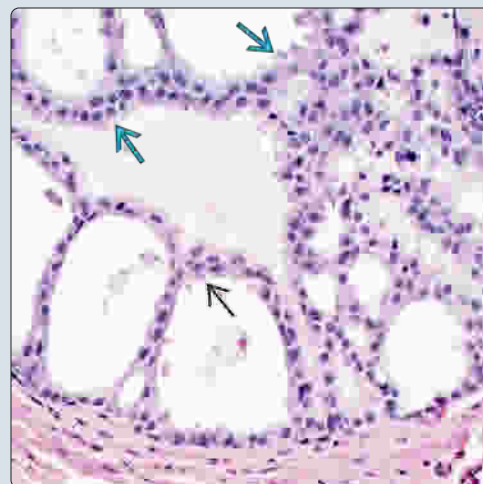
- Cystadenocarcinoma, salivary duct carcinoma, mammary analogue secretory carcinoma, acinic cell carcinoma, sclerosing polycystic adenosis

(Left) There is an unencapsulated tumor mass with predominantly cystic structures (enlarged ducts) of variable size. They are lined by a single layer of epithelial cells, which shows a more complex architecture in some foci. **(Right)** Multilayered epithelial proliferation shows "Roman bridges" Apocrine snouts are seen with abundant eosinophilic cytoplasm in the neoplastic cells. Secretions are noted in the lumen.

Unencapsulated Intraductal Proliferation



"Roman Bridge" Formation by Apocrine Cells

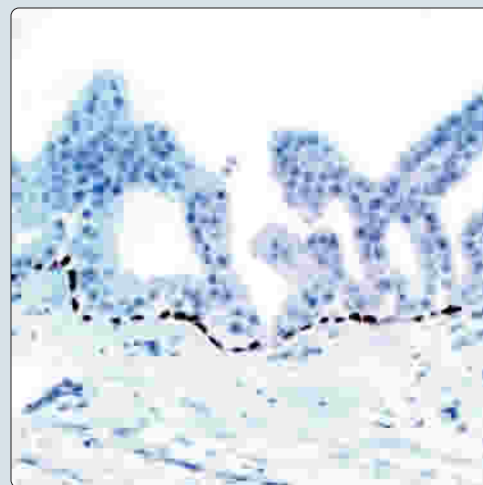


(Left) Single cells are noted lining the cystic spaces, with several small micropapillary structures projecting into the lumen. A myoepithelial layer at the tumor periphery is easily identified in this tumor. **(Right)** There is a strong nuclear p63 reaction in the myoepithelial layer that creates the periphery or external layer of the tumor.

Micropapillary Structures and Basal Cells



p63(+) Myoepithelial Layer



TERMINOLOGY

Abbreviations

- Low-grade intraductal carcinoma (LG-IDC)

Synonyms

- Low-grade cribriform cystadenocarcinoma; low-grade salivary duct carcinoma; intraductal carcinoma

Definitions

- Noninvasive (intraductal) salivary gland neoplasm with intracystic/intraductal growth resembling low-grade ductal carcinoma in situ of breast

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare
- Age
 - Older (mean: 62 years), but wide range (27-93 years)
- Sex
 - Female > male (1.5:1)

Site

- Major glands (parotid vast majority, 85%)

Presentation

- Nonspecific, painless swelling or mass in salivary gland

Treatment

- Surgery, with clinical follow-up to exclude progression

Prognosis

- Excellent long-term prognosis, although rare patients die from disease when invasion or lymph node metastases develop, often many years later

MACROSCOPIC

General Features

- Well circumscribed, nonencapsulated, dominated by multiple cystic spaces
- Most are < 2 cm

MICROSCOPIC

Histologic Features

- Nonencapsulated tumor with predominantly cystic structures (enlarged ducts) of variable size
 - Multicystic (multifocal), 1 or 2 cysts predominating
- Intraductal or intracystic epithelial proliferation
- Solid nests/islands, papillae, micropapillae, and loosely formed cribriform structures within cystic spaces
 - Cystically dilated ducts with tufted, micropapillary, anastomosing proliferations
 - Solid, lacy fenestrations or solid papillary proliferations
 - "Roman bridges" frequently seen
 - Cytoplasmic lipofuscin-type yellow-brown pigment
- Generally, no infiltration, desmoplasia, perineural or lymphovascular invasion
 - Fibrosis, hemorrhage, cholesterol clefts, and xanthic calcifications in stroma
- Low to intermediate nuclear grade; rarely high grade

- Nuclei are bland with evenly dispersed chromatin, small nucleoli
- Enlarged cells with granular, amphophilic to oncocytic cytoplasm
- Apocrine snouts with abundant eosinophilic cytoplasm
- Cysts contain eosinophilic debris and macrophages
- Comedonecrosis is generally absent, except if tumor shows high-grade cytology
- Myoepithelial layer surrounds tumor nests or islands
- ~ 25% will show microinvasion, suggesting tumor progression with time

ANCILLARY TESTS

Immunohistochemistry

- Luminal cells **positive**: S100 protein, AE1/AE3, CAM5.2, CK7, CK18, CK19, BRST-2, androgen receptor (AR) (60% of cases)
- Continuous rim of myoepithelial cells **positive**: p63, calponin, CK5/6, CK14, SMA, MSA
- **Negative**: CK20, ER, PR, p53, EGFR, Her-2/neu

DIFFERENTIAL DIAGNOSIS

Cystadenocarcinoma

- Controversial: Spectrum or distinct entity
- Complex, predominantly cystic, papillary epithelial proliferation with invasion
- Lacks solid and cribriform architecture; intermediate nuclear grade
- Lacks peripheral myoepithelial layer; **negative**: S100 protein

Salivary Duct Carcinoma

- Widely invasive, apocrine-type carcinoma, showing high-grade nuclear features, high mitotic index, comedonecrosis
 - Conceptually, in situ tumor may be precursor with intact myoepithelial layer
- **Positive**: AR; **negative**: CK5/6, p63; variable Her-2/neu

Mammary Analogue Secretory Carcinoma

- Cystic tumor with microvacuolar change, colloid-like secretions, and solid to papillary structures, but lacks "Roman bridges" and comedonecrosis
- Lacks peripheral myoepithelial layer
- **Positive**: S100 protein, mammaglobin, CK7, MUC4

Acinic Cell Carcinoma

- Papillary-cystic variant with cytoplasmic microvacuoles, pigment in cytoplasm, cytoplasmic granules
- **Negative** S100 protein and p63

Sclerosing Polycystic Adenosis

- Circumscribed, intraductal proliferation of acinar cells, cystic component, apocrine cells, sclerotic collagenous stroma

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3. Weinreb I et al: Low-grade intraductal carcinoma of salivary gland: report of 3 cases with marked apocrine differentiation. *Am J Surg Pathol.* 30(8):1014-21, 2006

Salivary Duct Carcinoma

KEY FACTS

TERMINOLOGY

- High-grade apocrine adenocarcinoma resembling subset of ER/PR(-) AR(+) breast ductal carcinoma (i.e., luminal AR[+])

CLINICAL ISSUES

- Represents ~ 10% of malignant tumors, whether de novo or part of carcinoma ex-pleomorphic adenoma
- Older at initial presentation; peak: 7th decade
- Male > female (2-4:1)
- Parotid gland is most commonly involved
- Aggressive multimodality therapy required
- Poor prognosis overall (< 45% 5-year survival)
- High rates of lymph node &/or distant metastases (60-70%)

MACROSCOPIC

- Unencapsulated, infiltrative tumor
- Average: 3.5 cm; range: 1-10 cm

MICROSCOPIC

- Perineural and lymph-vascular invasion are common
- Comedonecrosis is conspicuous
- Rounded to irregular, solid or cystic nodules of tumor cells
- Arranged in solid, band-like, papillary, and cribriform patterns; Roman bridge architecture is classic
- Polygonal cells with moderate/marked pleomorphism, ample eosinophilic, granular cytoplasm (apical snouts)
- Numerous mitoses, including atypical forms
- **Variants:** Sarcomatoid, micropapillary, mucin-rich, osteoclast-type giant cell

ANCILLARY TESTS

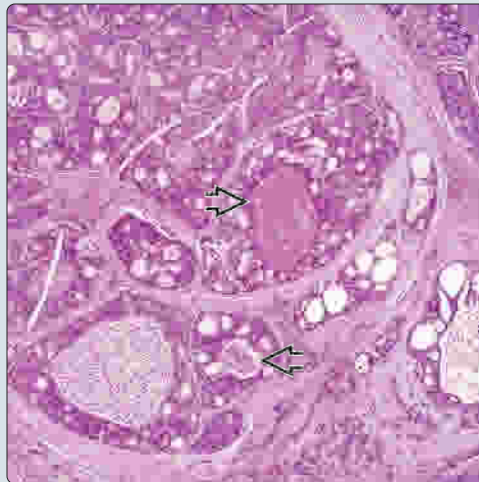
- **Positive:** AR, CK7; **negative:** CK5/6, p63

TOP DIFFERENTIAL DIAGNOSES

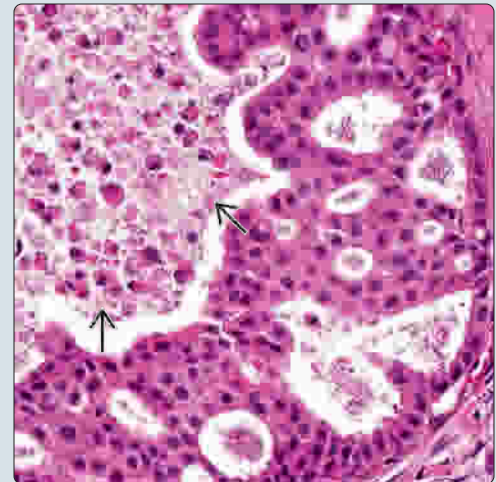
- Metastatic squamous cell carcinoma, mucoepidermoid carcinoma, high-grade transformation of salivary gland carcinomas, low-grade intraductal carcinoma

Cribriform and Glandular Profiles

(Left) Salivary duct carcinoma (SDC) is arranged in a glandular and cribriform architecture, here associated with comedonecrosis. This pattern is quite unique for SDC. (Right) A large duct is filled with a neoplastic proliferation that is arranged in the classic Roman bridge architecture. The center of the duct contains an area of comedonecrosis.

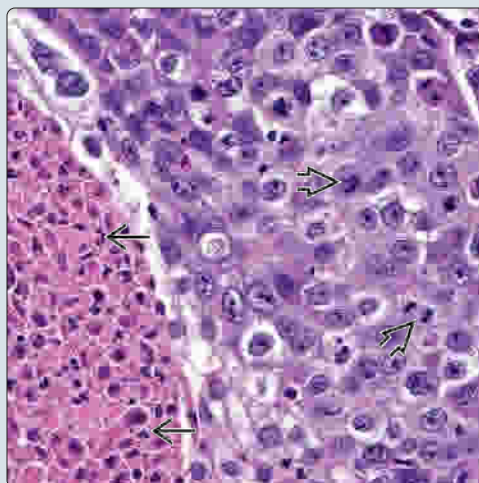


Roman Bridge Formation With Necrosis

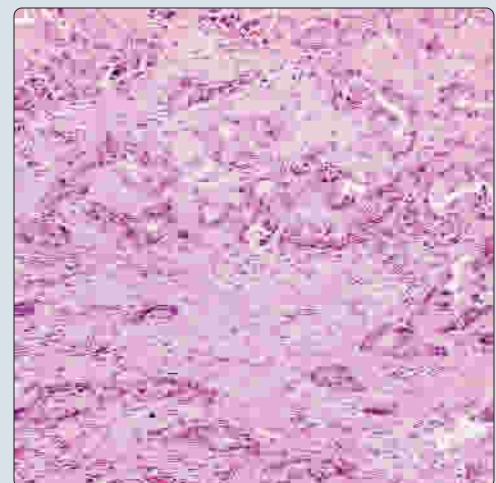


Pleomorphism With Necrosis

(Left) An area of comedonecrosis fills the center of this tumor nest. The cells show remarkable pleomorphism, prominent nucleoli, and mitotic figures. (Right) The neoplastic cells are associated with a strong, well-developed desmoplastic stromal reaction in this tumor.



Desmoplastic Stromal Reaction



TERMINOLOGY

Abbreviations

- Salivary duct carcinoma (SDC)

Definitions

- High-grade apocrine adenocarcinoma resembling a subset of ER/PR(-), AR(+) breast ductal carcinoma (i.e., luminal AR[+]) thought to be derived from intralobular and interlobular excretory ducts
 - Important to recognize as specific category/entity with clinical implications
- Low-grade cribriform cystadenocarcinoma vs. low-grade intraductal carcinoma are different tumors

ETIOLOGY/PATHOGENESIS

Neoplastic Transformation

- More than 50% of SDCs arise within pleomorphic adenoma

CLINICAL ISSUES

Epidemiology

- Incidence
 - Represents ~ 10% of malignant salivary gland tumors
 - Whether de novo or part of carcinoma ex-pleomorphic adenoma
- Age
 - Older at initial presentation; peak: 7th decade
- Sex
 - Male > female (2-4:1)

Site

- Parotid gland is most commonly involved (~ 70-95% of cases)
- Submandibular, minor salivary gland (palate specifically), and rarely sublingual gland

Presentation

- Swelling or mass with recent rapid growth of parotid gland
- Majority of patients experience facial nerve paresthesia, pain, paresis, palsy, or paralysis
- Surface ulceration may be seen
- Cervical lymphadenopathy is present in ~ 1/3 of patients at initial presentation
 - Subsequently, most patients will develop lymph node metastases
- Since SDC develops within pleomorphic adenoma, symptom duration may be overestimated

Treatment

- Aggressive multimodality therapy required
- Radical excision to include lymph node dissection
- Radiotherapy (usually 60 Gy) combined with surgery
- Various chemotherapies are investigational
 - Androgen deprivation therapy
 - Trastuzumab (Herceptin) therapy for HER2/neu FISH positive tumors, especially with intact *PIK3CA* pathway
 - HER2/neu detected by IHC only may not correspond to therapeutic response
 - *PIK3CA* pathway potential therapeutic target

Prognosis

- Poor prognosis overall (< 45% 5-year survival)
 - 1 of the most aggressive salivary gland malignancies
- Local recurrences in up to 50%
- Most patients present with stage III or IV disease
- High rates of lymph node &/or distant metastases (60-70%)
 - Early distant metastases is rule
 - Lymph node metastases correlate with worse prognosis
 - Presence of nodal metastases predicts distant metastases
 - Distant sites include lung, bone, liver, spleen, skin, adrenal glands, kidney, brain
- Poor prognostic indicators
 - Size > 3 cm; positive surgical margin status, > 50 years of age
 - Lymphovascular &/or perineural invasion; lymph node &/or distant metastases; micropapillary pattern
 - Positive HER2/neu overexpression
- **No** correlation with outcome: p53 protein (controversial), DNA aneuploidy, increased proliferative activity

IMAGING

Radiographic Findings

- Ill-defined margins, frequently showing central necrosis
- Calcifications suggest residual pleomorphic adenoma

MACROSCOPIC

General Features

- Unencapsulated and poorly circumscribed, infiltrative tumor
- Multinodularity is common
- Cut surface is firm, solid, grayish white to yellowish white
- Cysts, necrosis and fibrosis are frequently seen
- Macroscopic features of concurrent/preexisting pleomorphic adenoma may be seen

Size

- Average: 3.5 cm; range: 1-10 cm

MICROSCOPIC

Histologic Features

- Frequently, SDC is malignant component of carcinoma expleomorphic adenoma
- Variably sized, rounded, solid or cystic nodules of tumor cells that resemble intraductal or infiltrating ductal carcinoma of breast
- Small nodules (2x diameter of interlobular salivary gland ducts) are filled with neoplastic cells
- Larger cystic nodules with irregular shape
- Comedonecrosis is conspicuous (central-intraductal type or filling cystic spaces)
- Perineural invasion (60%) and vascular invasion (31%) are frequent
- Extraglandular/parenchymal extension with positive surgical margins
- Marked, dense, desmoplastic (hyalinized) fibrosis is conspicuous
- Lymphoplasmacytic inflammatory cell infiltrate is frequently present

- Cells are arranged in cribriform, band-like solid, and papillary patterns
 - Roman bridge architecture is classic
- Small tumor nests infiltrate between larger nodules
 - Nonneoplastic glandular parenchyma is absent between nodules
- Epithelial cells have moderate to marked pleomorphism, are cuboidal to polygonal, with ample eosinophilic, granular, oncocytic cytoplasm
 - Although often monotonous in any single tumor
 - Show classical features of apocrine neoplasm
 - Nuclei are round, centrally located, with large, prominent nucleoli and hyperchromatic chromatin
- Mitotic figures are usually easily identified, including atypical forms
- Psammoma bodies and areas of squamous differentiation are rare

Lymph Nodes

- Positive in 60-70% of cases, many at presentation

Variants

- All variants still have histopathologic features of typical SDC
- Minimal proportion of **variant** morphology required to diagnose "variant" is not quantified
- **Sarcomatoid**
 - Biphasic neoplasm composed of both SDC and sarcomatoid (spindle cell) elements
 - Dyscohesive, pleomorphic population, predominantly spindled
 - Concurrent heterologous elements (bone, cartilage) can be seen
 - Sarcomatous areas **positive**: EMA, CK4 (focal in ~ 50%), p53 (diffuse in ~ 30% of cases)
- **Micropapillary**
 - Invasive micropapillary architecture
 - Morula-like small epithelial cell clusters without fibrovascular cores surrounded by clear space
 - Eosinophilic cytoplasm, with apocrine-type apical globules of cytoplasm
 - **Positive**: CK7, EMA (distinctive inside-out pattern), Ki-67 (high index)
- **Mucin rich**
 - SDC with malignant cell nests floating in pools of extracellular epithelial mucin
- **Osteoclast-type giant cell**
 - Osteoclast-like giant cells resembling giant cell tumor of bone
 - Mononuclear cells are immunoreactive for epithelial markers and androgen receptors

ANCILLARY TESTS

Cytology

- Cellular smears with abundant background debris and necrotic material
- Epithelial tumor cells arranged in cohesive clusters, cribriform pattern or 3D papillary clusters
- Isolated, individual atypical epithelial cells scattered at periphery of clusters
- Round, polygonal to spindled tumor cells with abundant, finely granular to vacuolated cytoplasm

- Medium to large, pleomorphic, and hyperchromatic nuclei with prominent nucleoli

Histochemistry

- Nonreactive with mucicarmine and Alcian blue

Immunohistochemistry

- **Positive**: Androgen receptor, CK7; **negative**: CK5/6, p63

In Situ Hybridization

- *PTEN* loss in 50%: Homozygous or hemizygous deletion, chromosome 10 monosomy
- *ERBB2* (*HER2/neu*) gene amplification detected by FISH (10-30%)
 - High gene amplification (10+ copy number) correlated to 3+ IHC staining

Genetic Testing

- Mutations/amplification of gene encoding p110- α catalytic subunit of phosphoinositide 3-kinase (*PIK3CA*) &/or loss of phosphatase and tensin homolog (*PTEN*) are known to activate the phosphoinositide 3-kinase (PI3K) pathway
 - *PIK3CA* exons 9 or 20 mutations are most frequent
- *EGFR* mutations: ~ 10% of tumors (exons 18 and 19)
 - **No** positive correlation between *EGFR* and *ERBB2* (*HER2/neu*) alterations (independent roles)
- *HRAS* hotspot mutations detected in ~ 30%
- No *PIK3CA*, *EGFR*, or *AR* gene amplification
- Both *PIK3CA* mutation and *PTEN* loss may be seen (not mutually exclusive)

DIFFERENTIAL DIAGNOSIS

Squamous Cell Carcinoma (Metastatic)

- Sheets of tumor cells with opacified cytoplasm, intercellular bridges, hyperchromatic nuclei
- **Positive**: p63, p40, CK5/6; **negative**: AR

Mucoepidermoid Carcinoma, High Grade

- Lacks prominent papillary or cribriform patterns, showing mucocytes, epidermoid cells, and transitional areas
- **Positive**: CK5/6, p63; **negative**: AR

High-Grade Transformation of Salivary Gland Carcinoma

- Any primary salivary gland carcinoma that undergoes high-grade transformation may mimic SDC
- Generally, focal areas of lower grade tumor will be seen
- Selected IHC panels applied to document true tumor type

Low-Grade Intraductal Carcinoma (Cribriform Salivary Duct Carcinoma)

- Controversial entity with cribriform and Roman bridge architecture, but usually duct confined, with low nuclear grade and no necrosis
- Much better prognosis than conventional SDC
- **Positive**: S100 protein, AR, with basal p63 and CK5/6

Metastatic Breast or Prostate Carcinoma

- Very rare, with clinical/radiographic history of breast or prostate primary
- Circumscribed tumor nodules, Roman bridge cribriform architecture, ductal structures, comedonecrosis, and pleomorphism seen in both

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
Androgen receptor	Positive	Nuclear	Strong reaction > 98% of tumors
CK-PAN	Positive	Cytoplasmic	Most tumor cells
GATA3	Positive	Nuclear	Strong, diffuse, nearly all tumor cells
CK7	Positive	Cytoplasmic	Most tumor cells
EMA	Positive	Cell membrane & cytoplasm	
CEA-M	Positive	Cytoplasmic	
Cyclin-D1	Positive	Nuclear	Strongly overexpressed in most tumor cells
HER2	Positive	Cell membrane	Strong, diffuse, linear membrane reactivity in > 30% of tumor cells; present in up to 50% of tumors
EGFR	Positive	Cell membrane	Most tumors have positive reaction but not gene amplification; ~ 10% have mutations
GCDPF-15	Positive	Cytoplasmic	Strong, but focally immunoreactive
PSA	Positive	Cytoplasmic	< 5% of tumors
p63	Negative		Only highlights myoepithelial/basal cells in most tumors
CK14	Positive	Cytoplasmic	Only in myoepithelial cells surrounding "ducts" or large spaces (but interpret with caution)
Calponin	Negative		Only in myoepithelial cells surrounding "ducts" or large spaces (but interpret with caution)
Actin-sm	Negative		Only of myoepithelial cells surrounding "ducts" or large spaces (but interpret with caution)
ER	Positive	Nuclear	Variable, but limited usually
PR	Negative		
S100	Negative		
Bcl-2	Negative		
DOG1	Negative		

o Sialodochodysplasia would exclude metastatic disease

- **Breast: Positive:** ER, PR; **negative:** AR (usually)
- **Prostate: Positive:** PSA, PAP, AR, Erg

Cystadenocarcinoma

- Different from **cribriform cystadenocarcinoma**
- Predominantly papillary, cystic tumor, with low-grade cytologic features, lacking infiltration and comedonecrosis

Oncocytic Carcinoma

- Abundant, granular eosinophilic cytoplasm seen in both
- Lacks cystic, papillary, and cribriform patterns, with oncocytes tending to be larger
- Comedonecrosis is usually absent
- Plentiful mitochondria (PTAH or EM); **negative:** AR

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CT of CEPA, Salivary Duct Carcinoma

(Left) CT shows a left parotid gland mass. There is cystic degeneration and necrosis within the central portion of the mass. Note the calcification, which suggests a previous pleomorphic adenoma, confirmed histologically. (Right) This man shows a large, ulcerated mass just below the ear, a site quite common for parotid gland tail tumors. It is easy to see how this could be misconstrued as a primary skin-based tumor.

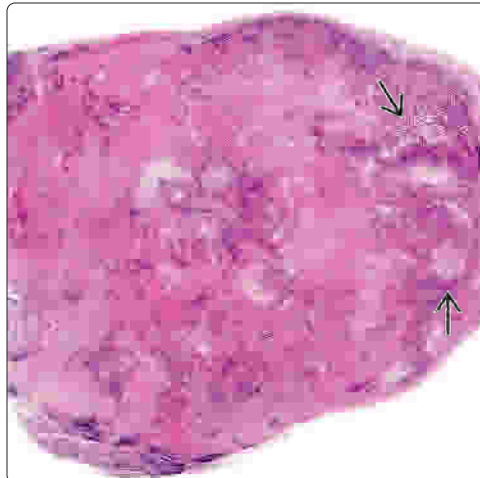


Ulcerated Large Parotid Gland Mass

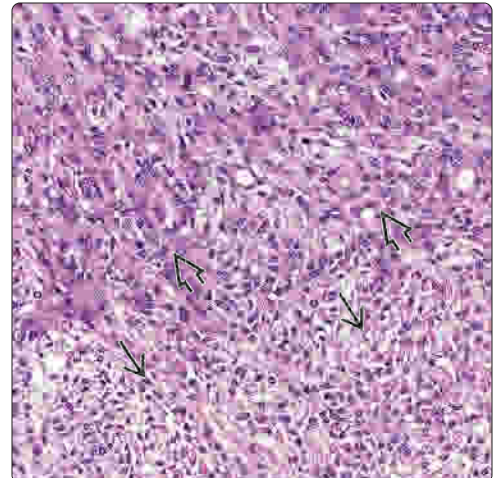


CEPA With Salivary Duct Carcinoma

(Left) SDCs are usually large, in this example subtotally replacing the parotid gland. There is a vague nodularity, and areas of necrosis and fibrosis are frequent, as seen in this low-power view. A is noted. Note the concurrent pleomorphic adenoma. (Right) H&E shows a transition between a pleomorphic adenoma (PA) and a SDC. There is an imperceptible blending between these tumors in this field.

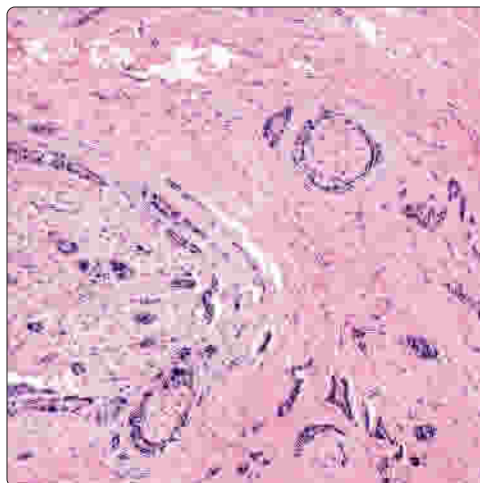


Transition Between Pleomorphic Adenoma and Salivary Duct Carcinoma

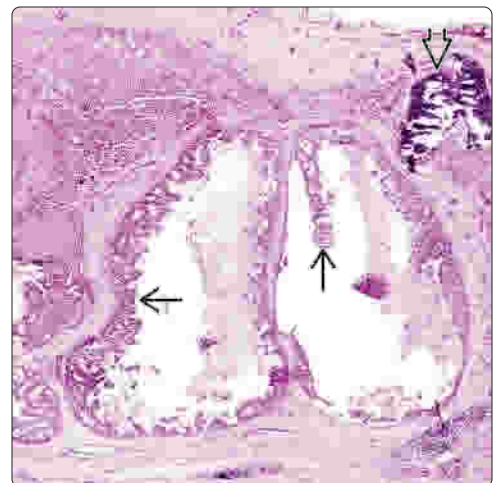


Perineural Invasion by Neoplastic Cells

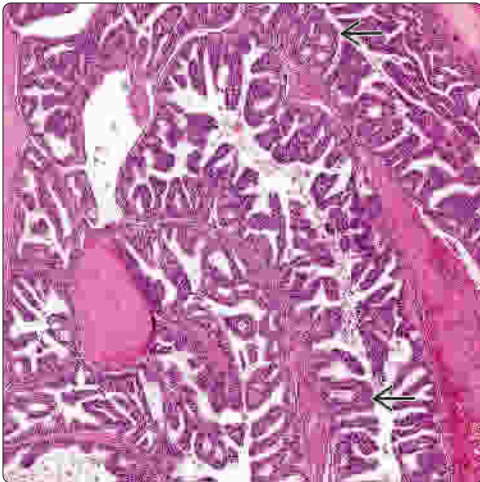
(Left) SDC will very frequently have a significant and well-developed peri- and intraneural invasion, as illustrated in this case. (Right) There are solid areas as well as large cystic spaces within this SDC. Note the papillary projections as well as areas of calcification. These are common findings in SDC.



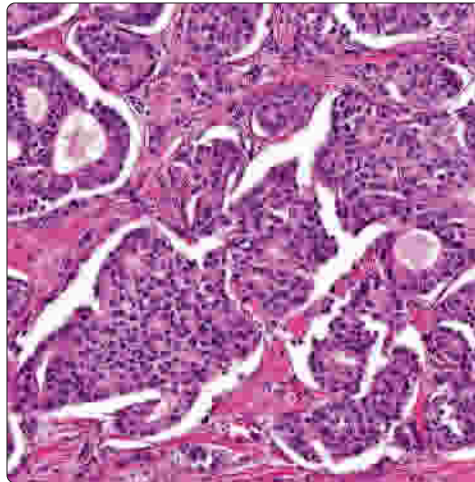
Large and Small Cysts Within Tumor



Papillary and Roman Bridge Formations



Ductal Appearance With Limited Atypia

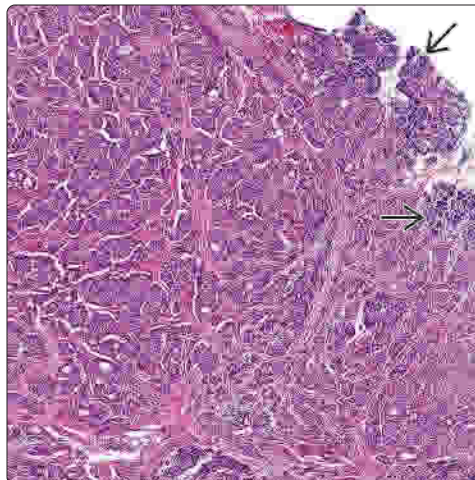


(Left) The neoplasm is typically arranged in cribriform, band-like solid regions and papillary patterns. This field demonstrates a large number of papillae, although areas of Roman bridge formation are also noted [1]. **(Right)** Small nodules of tumor cells create a ductal appearance. Note the separation by heavy fibrous connective tissue stroma. There is cellular monotony in this area, even though all the cells are atypical.

Roman Bridge Formation

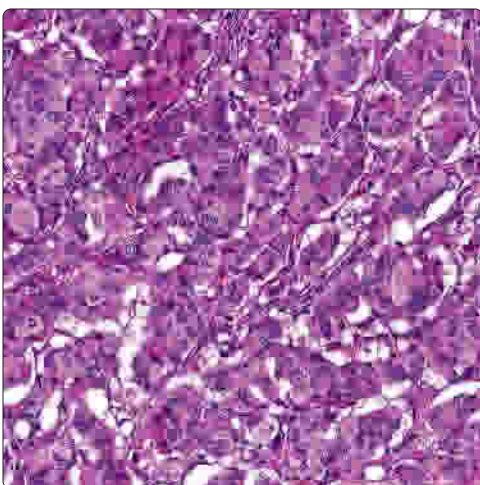


Micropapillary Pattern With Invasion

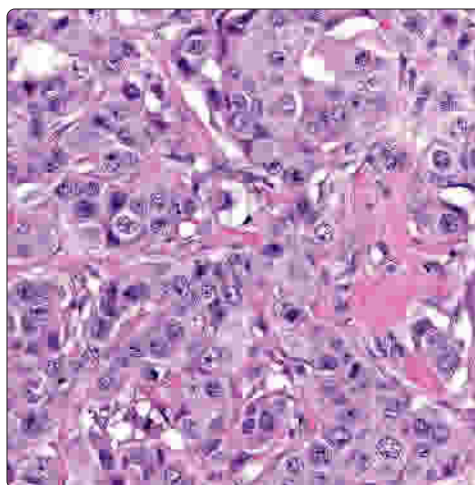


(Left) There is a well-developed Roman bridge formation in this example of SDC. There is mucinous differentiation as well as a hint of a basal cell zone [2], the area that would be p63 and CK5/6 positive. **(Right)** There is a micropapillary pattern to this SDC that demonstrates infiltration into the adjacent parotid gland parenchyma [3]. The tumors tend to lack well-formed capsules and are widely invasive.



Apocrine Appearance



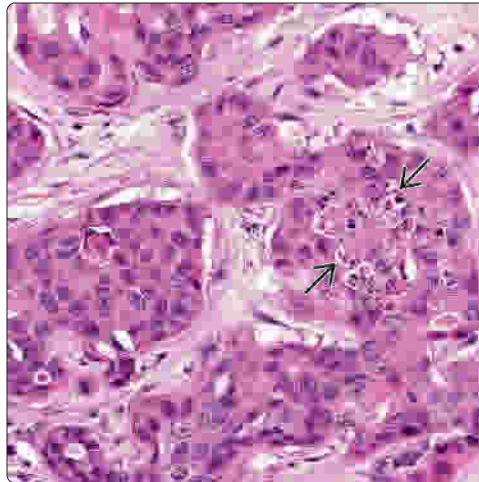
Apocrine Cells With Pleomorphism



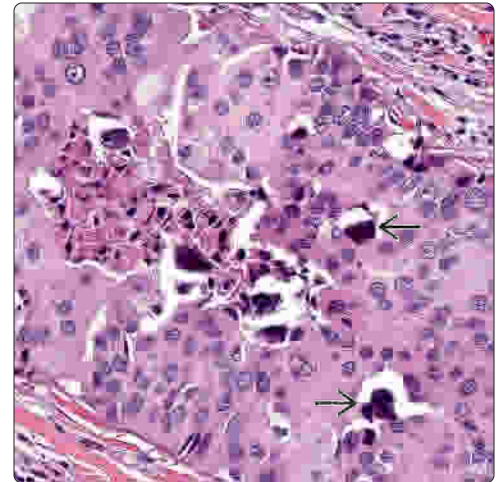
(Left) Multiple small packets of neoplastic cells are noted in this area, with ample eosinophilic cytoplasm giving an apocrine appearance. Retraction artifacts are commonly seen in SDC, and should not be construed as lymphovascular invasion. **(Right)** The epithelial cells have moderate to marked pleomorphism, showing polygonal cells with ample eosinophilic, granular cytoplasm. Nucleoli are easily identified in most of the tumor cells.

(Left) The neoplastic cells are arranged in small nests with the polygonal cells showing moderate pleomorphism. The cytoplasm is granular to opacified. Note the area of comedonecrosis . **(Right)** The neoplastic cells show an apocrine morphologic appearance with abundant cytoplasm. Note the areas of calcification  along with areas of comedonecrosis in this SDC.

Focal Comedonecrosis

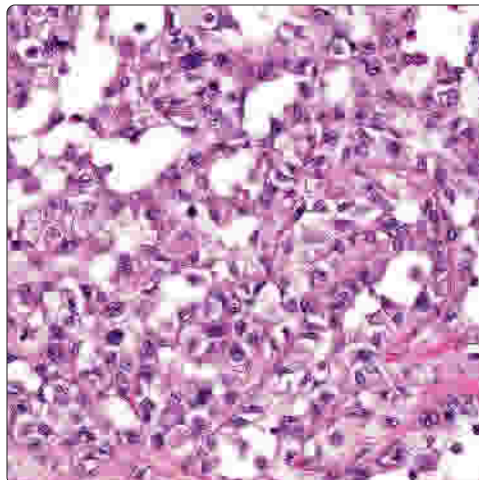


Necrosis With Calcifications

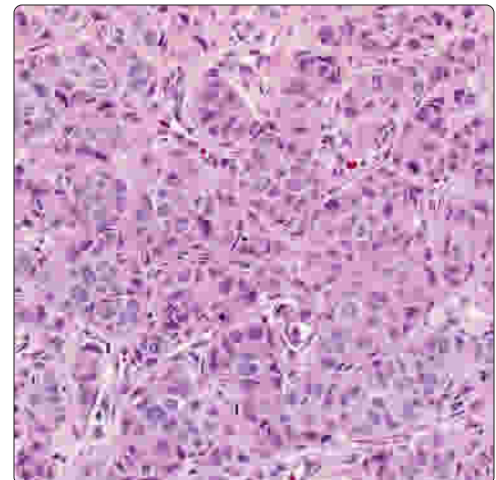


(Left) There is a clearing to the cytoplasm in this particular area of an SDC, although it is infrequently observed. The tumor is arranged in a cribriform to glandular pattern. **(Right)** This nested pattern shows cells with a high nuclear:cytoplasmic ratio but with limited pleomorphism. The nuclear chromatin is delicate and even with small nucleoli.


Focal Cytoplasmic Clearing

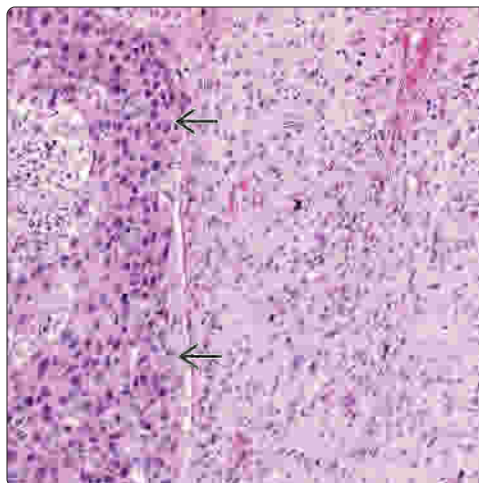


Nested Pattern of Growth

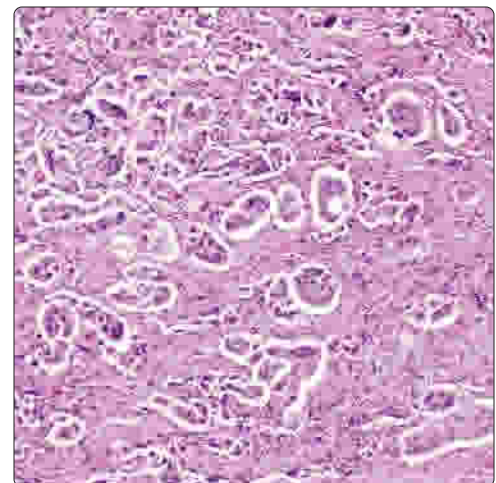


Biphasic Sarcomatoid Salivary Duct Carcinoma

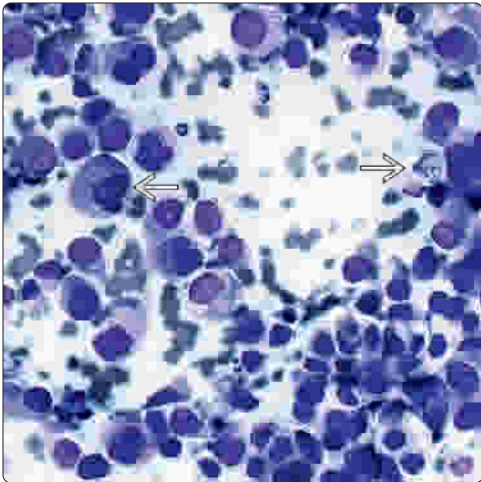
(Left) Biphasic neoplasms, such as this one, are composed of epithelial and spindle cell elements in a sarcomatoid SDC. The epithelial cells  are cohesive sheets, separated from the fascicles of spindled cells. Mitoses are increased. **(Right)** This neoplasm shows a micropapillary architecture, which shows small nests of cells without any true fibrovascular cores noted within a dense and cellular stroma.



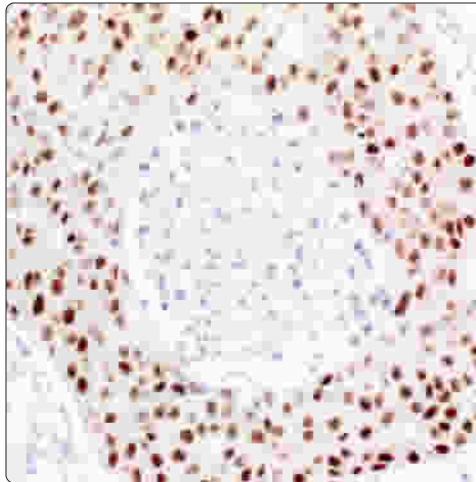
Micropapillary Pattern




Highly Pleomorphic Tumor Cells in Fine-Needle Aspiration

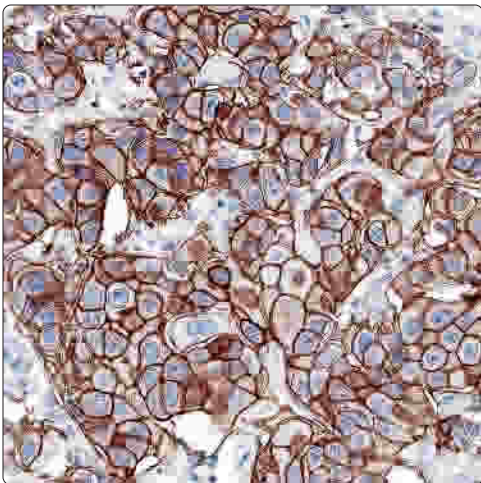


Androgen Receptor With Strong Nuclear Reaction

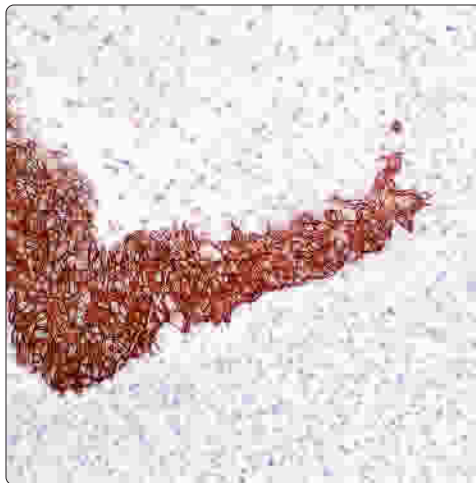


(Left) There are numerous dyscohesive neoplastic cells in this fine-needle aspiration smear of a parotid gland SDC. There are mitoses  along with marked nuclear variability (pleomorphism). **(Right)** Androgen receptor is nearly ubiquitously present in SDC, showing a strong and diffuse nuclear reaction in nearly all tumor cells.

HER2/neu Membrane Reaction

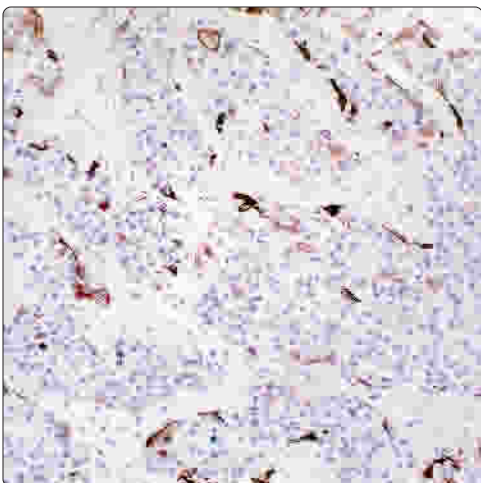


HER2/neu Membrane Reaction

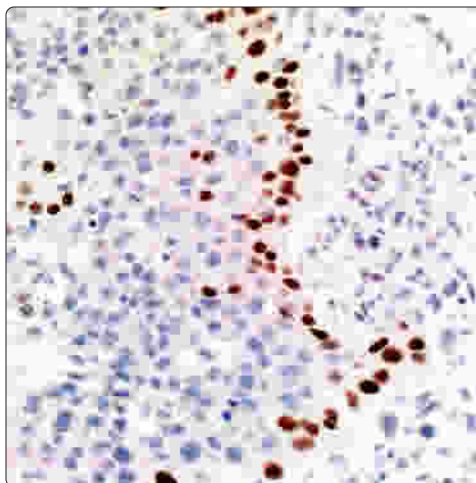


(Left) Similar to breast carcinoma, SDC with HER2/neu staining shows a strong, diffuse membrane reactivity circumferentially highlighting the neoplastic cells in > 30% of the tumor cells. There is occasionally amplification by FISH. **(Right)** The neoplastic epithelial cells in this sarcomatoid SDC show a strong and diffuse membranous reactivity with HER2/neu. This is the type of reaction that could potentially show molecular-based mutations/amplification.

CK5/6 Highlights Rare Basal Cells



p63 Highlights Basal Cells in Salivary Duct Carcinoma



(Left) CK5/6 is shown here to highlight several basal cells are the periphery of the tumor nests in this SDC. There is usually not a strong or diffuse reaction. **(Right)** In general, the neoplastic cells of a SDC are negative with p63. However, the basal cells at the periphery of the tumor nests can be positive, as highlighted in this case.

Epithelial-Myoepithelial Carcinoma

KEY FACTS

TERMINOLOGY

- Malignant neoplasm demonstrating biphasic pattern of inner duct-like and outer layer of myoepithelial-like cells

CLINICAL ISSUES

- ~ 1% of all salivary gland tumors
- Female > male (2:1)
- Major salivary glands most common
- Good overall prognosis
 - Recurrences in up to 50%

MACROSCOPIC

- Nodular or multinodular mass, with irregular borders

MICROSCOPIC

- Classic features of biphasic (bilayered) tubular histology, which predominates
- **Inner layer** formed by single row of cuboidal to columnar epithelial cells

- **Outer layer** formed by myoepithelial cells arranged in multiple layers of large polygonal cells with indistinct borders
 - Clear cytoplasm, surrounding vesicular nucleus
- Basement membrane-like hyalinized material may separate duct-like structures
- **Rare** findings: Squamous &/or sebaceous differentiation; spindle cell pattern; ancient change; Verocay-like change
- Oncocytic and apocrine variants show biphasic patterns
- High-grade transformation (dedifferentiation) (~ 2%)

ANCILLARY TESTS

- Epithelial and myoepithelial markers highlight dual population

TOP DIFFERENTIAL DIAGNOSES

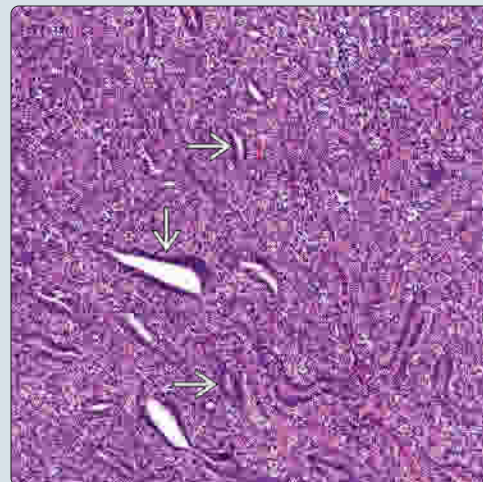
- Benign: Pleomorphic adenoma, myoepithelioma
- Malignant: Clear cell carcinomas (acinic cell, mucoepidermoid and hyalinizing), myoepithelial carcinoma

Multinodular Growth

(Left) On low power, there is a well-defined but unencapsulated tumor showing a multinodular appearance with irregular borders. Bands of fibrosis dissect the tumor. **(Right)** Epithelial-myoepithelial carcinoma (EMC) shows classic biphasic (bilayered) tubular histology. More hyperchromatic, inner ductal cells are noted ➡ surrounded by myoepithelial clear cells.

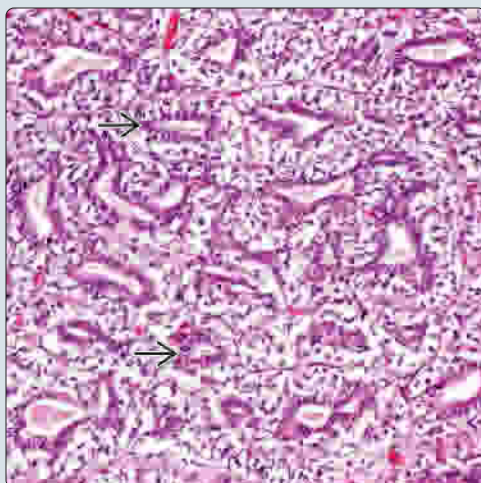


Characteristic Histology

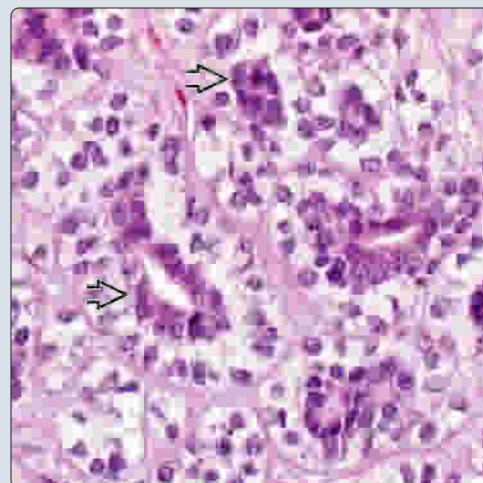


Myoepithelial Cytoplasmic Clearing

(Left) The myoepithelial population is abluminal and characteristically shows a very clear cytoplasm. Nuclei may be spindled. The ductal component shows luminal cuboidal cells ➡. **(Right)** The inner layer is formed by a single row of cuboidal epithelial cells ➡ around a lumen. The outer layer is formed by large polygonal myoepithelial cells with clear cytoplasm and indistinct borders. This is the most characteristic appearance of EMC.



High-Power Biphasic Appearance



TERMINOLOGY

Abbreviations

- Epithelial-myoepithelial carcinoma (EMC)

Definitions

- Malignant neoplasm demonstrating variable proportions of biphasic pattern of inner luminal epithelial duct-like cells and outer abluminal layer of myoepithelial-like cells

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~ 1% of all salivary gland tumors
 - ~ 2% of all salivary gland malignancies
- Age
 - Peak: 6th to 7th decades
 - Rare in children
- Sex
 - Female > male (2:1)

Site

- Major salivary glands most common: Parotid gland: ~ 70%; submandibular gland: ~ 12%
- Minor salivary glands (~ 18%): Upper and lower respiratory tracts, palate

Presentation

- Slow-growing, painless mass
- Tumors are frequently present for years
- Minor salivary gland lesions present as submucosal nodule
- Rarely, tumors with high-grade transformation may present with rapid growth and pain, along with facial nerve palsy

Treatment

- Surgical approaches
 - Complete resection

Prognosis

- Usually good overall prognosis (low-grade tumor)
 - 90% 5-year survival
 - 75% 10-year survival
- Recurrences in up to 50%
 - Recurrences usually develop within 5 years
 - Univariate predictors of recurrence
 - Margin status, angiolymphatic invasion, tumor necrosis, myoepithelial anaplasia
- Distant metastases in up to 20%
 - Cervical lymph nodes, lung, liver, and kidney
- Death from disease in ~ 10% of cases
- Poorer prognosis associated with minor salivary gland tumors, rapid tumor growth, large tumor size, solid growth, nuclear pleomorphism, high proliferation index, aneuploidy, and high-grade transformation

MACROSCOPIC

General Features

- Well-defined but unencapsulated mass
- Nodular or multinodular mass, with irregular borders
- Minor salivary gland tumors are poorly defined
- Tumors are firm, gray-tan-white

- Cystic areas may be seen on cut surface

Size

- Range: 2-12 cm; mean: 2.5 cm

MICROSCOPIC

Histologic Features

- Lobules of tumor
- Surface ulceration (minor salivary gland tumors) in ~ 40% of cases
- Classic features of biphasic (bilayered) tubular histology, which predominates
 - **Inner layer** formed by single row of cuboidal to columnar epithelial cells
 - Dense to finely granular cytoplasm surrounding round to oval nucleus
 - Duct cells are intercalated duct-like
 - **Outer layer** formed by myoepithelial cells
 - Large polygonal cells with indistinct borders arranged in multiple layers
 - Clear cytoplasm around eccentric, vesicular nucleus
 - Rich in glycogen (diastase-sensitive PAS[+])
- Clear cells may dominate, with only isolated duct-lining cells (without canalization)
 - Luminal cells comprise up to ~ 1/3 of cell population
- Proteinaceous material may be seen in lumen
 - PAS positive but not mucicarmine positive
- Mixture of tubular, glandular, and solid patterns
 - Organoid or thèque-like pattern can be seen
 - Solid, spindled cell population may be present
- Papillary and cystic areas comprise small proportion of some tumors (20%)
- Pleomorphism is mild for vast majority
- Basement membrane-like hyalinized material may separate duct-like structures
- Perineural and vascular invasion are common
 - Bone invasion is uncommon
- Mitotic figures are sparse (1-2/10 HPFs)
- **Rare** findings: Squamous &/or sebaceous differentiation; spindle cell pattern; ancient change; Verocay-like change
- Rare malignancy in carcinoma ex-pleomorphic adenoma
- Oncocytic variant: Develop in patients a decade later (compared to classic EMC), frequently papillary, calcifications seen, sebaceous components present
- Apocrine variant: Apocrine ductal components, cribriform to solid patterns, positive with androgen receptors, GCDPF15, but still biphasic
- High-grade transformation (dedifferentiation) (~ 2%)
 - Mean age 72 years, parotid most common, epithelial >> myoepithelial, and poor prognosis
 - Sheets and nests of markedly atypical cells showing necrosis, increased mitoses
 - Areas of typical EMC still identified

ANCILLARY TESTS

Cytology

- One of the tumors with high false-negative rate
- Biphasic smears with ductal cells and larger clear cells
- Larger cells are fragile, creating naked nuclei
- Hyalinized basal lamina can create globules

Immunohistochemistry Table

Antibody	Reactivity	Staining Pattern	Comment
CK-PAN	Positive	Cytoplasmic	Ductal cells specifically
EMA	Positive	Cytoplasmic	Ductal cell specifically
CK5/6	Positive	Cytoplasmic	Variably present, ductal and myoepithelial cells
p63	Positive	Nuclear	Myoepithelial cells only
Actin-sm	Positive	Cytoplasmic	Myoepithelial cells only
Calponin	Positive	Cytoplasmic	Myoepithelial cells only
CK14	Positive	Cytoplasmic	Myoepithelial cells only
SMHC	Positive	Cytoplasmic	Myoepithelial cells only
S100	Positive	Nuclear & cytoplasmic	Myoepithelial cells predominantly
SOX10	Positive	Nuclear	All neoplastic cells
DOG1	Positive	Cell membrane	Membranous reaction in abluminal myoepithelial cells; apical-luminal staining of ductal cells
Nestin	Positive	Cytoplasmic	Abluminal (myoepithelial) cells only
Vimentin	Positive	Cytoplasmic	Preferentially myoepithelial cells
CD117	Positive	Cytoplasmic	Variably present, highlighting myoepithelial cells specifically
p53	Positive	Nuclear	Only in tumors with dedifferentiation
GFAP	Equivocal	Cytoplasmic	Myoepithelial cells occasionally

Histochemistry

- PAS highlights basement membrane material and glycogen (with diastase) in myoepithelial cells

Immunohistochemistry

- Epithelial and myoepithelial dualism highlighted by appropriate selected immunohistochemistry

DIFFERENTIAL DIAGNOSIS

Pleomorphic Adenoma

- Multinodular and bosselated growth with biphasic epithelial/myoepithelial populations
- Myxochondroid matrix material merged or blended with epithelial population, not sharp separation
- Bilayered tubule formation is **not** prominent, nor is clear cell population

Adenoid Cystic Carcinoma (ACC)

- Cribriform pattern (common in ACC) not seen in EMC
- Cells are small, with peg-shaped or carrot-shaped very hyperchromatic nuclei

Myoepithelioma/Myoepithelial Carcinoma

- Spindled cell neoplasm **without** ductal or tubule formation

Mucoepidermoid Carcinoma

- Problems with clear cell variant, specifically
- Cyst formation, mucocytes, and transitional pattern seen somewhere in tumor, lacking biphasic pattern

Clear Cell Acinic Cell Carcinoma

- Lacks biphasic appearance
- Clear cell areas tend to be small and nondominant
- Basophilic, granular cytoplasm predominates in most
- High glycogen content is not seen
- No myoepithelial phenotype immunohistochemically

Hyalinizing Clear Cell Adenocarcinoma

- Predilection for minor salivary gland (intraoral) sites
- Monotonous cells, lacking myoepithelial cells
- Small islands and single cell infiltration associated with prominent fibrous connective tissue stroma

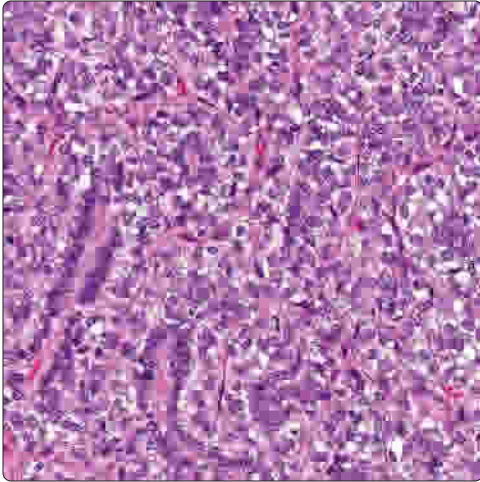
Oncocytoma, Clear Cell Type

- Large polygonal cells without biphasic appearance
- Clear cell changes may predominate, but oncocytic, granular cytoplasm is still found

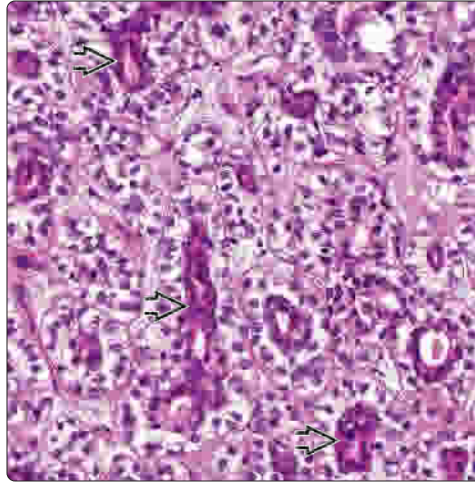
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Biphasic but Solid Growth



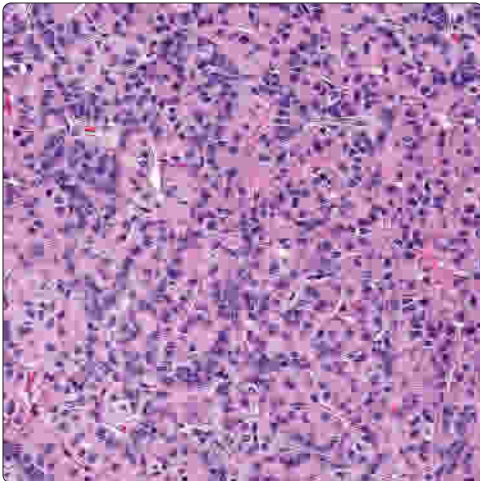
Characteristic Biphasic Appearance



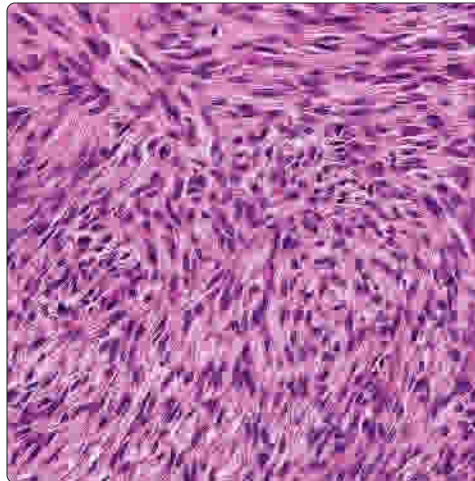
(Left) The tumor will frequently display a cellular, solid pattern. However, the characteristic bilayered tubule formation is easily detected. The outer myoepithelial cells have cleared cytoplasm.

(Right) Tumor nests, which have the characteristic central duct-like structures (cuboidal cells) [E], surrounded by the syncytial arrangement of myoepithelial cells with clear cytoplasm, are encased by delicate wisps of stroma.

Solid Pattern in EMC

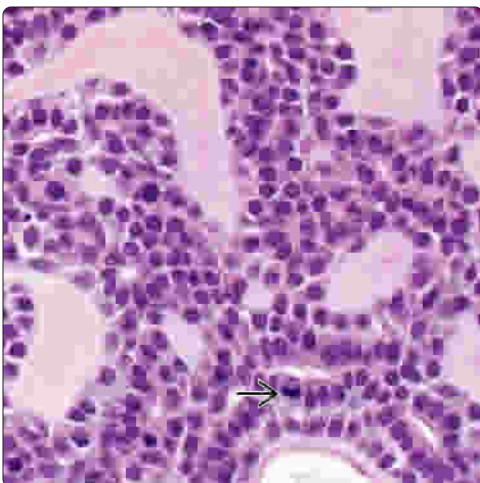


Spindle Cell Morphology

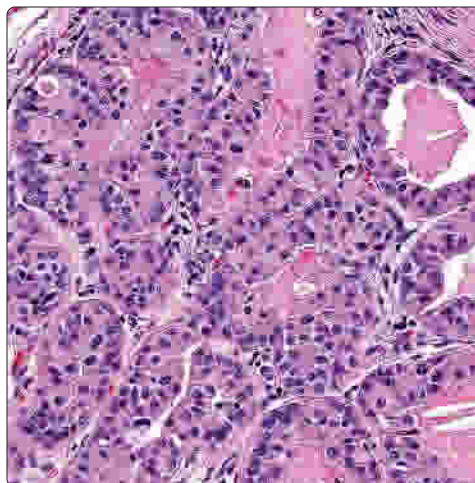


(Left) There is a more sheet-like or solid pattern to this tumor. However, darker cells are noted adjacent to the areas of more eosinophilic appearance. This tumor had areas of more classic biphasic appearance elsewhere. **(Right)** Spindled myoepithelial cells are a common finding, although in general this is not a dominant pattern of growth. A vaguely fascicular architecture (Verocay-like) is suggested here. If this were the only pattern in the tumor, it would be a myoepithelioma/myoepithelial carcinoma.




Solid to Tubular Growth



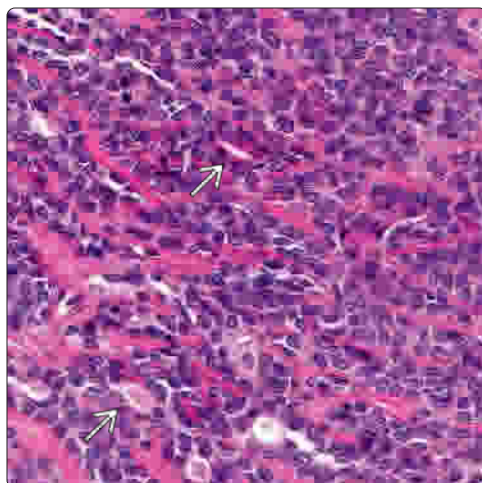
Glandular Pattern in EMC



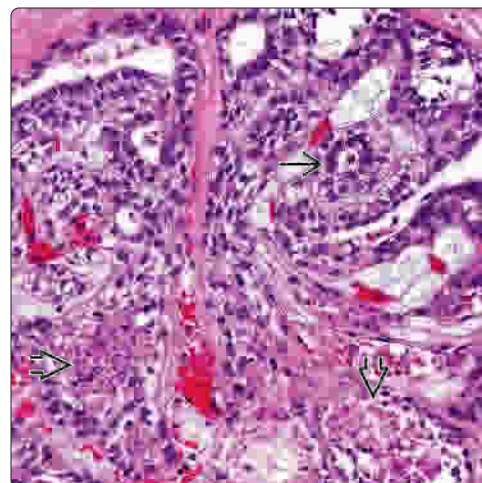
(Left) There is a more solid appearance, with basement membrane-type material. This pattern can mimic basal cell adenoma (a potential cause for false-negative rate on cytology). Note the mitosis [E], which are usually sparse in EMC. **(Right)** Although the clear cell change in the myoepithelial cells usually predominates, there are tumors that lack this feature. Secretions in the lumen of these ducts do not stain with mucicarmine. There is a moderate degree of nuclear pleomorphism.


(Left) The histologic resemblance of this single high-power field to a basal cell adenoma is quite remarkable. Basement membrane-like hyalinized material is seen separating the duct-like structures. However, the biphasic appearance can still be seen  if carefully evaluated. **(Right)** Tumor cell necrosis  is not a frequent feature in this tumor, although there can be isolated foci in some tumors. Note the characteristic biphasic tubule formation elsewhere .

Basement Membrane-Like Material

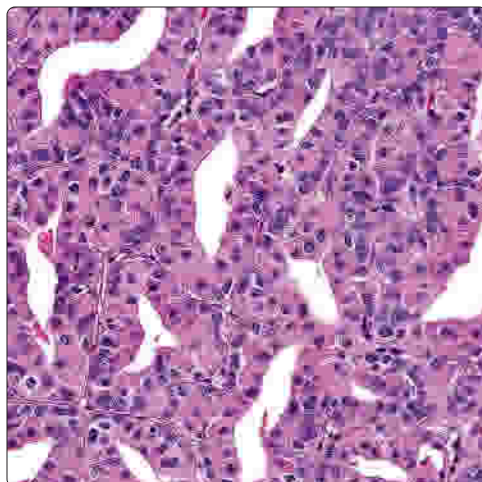


Tumor Necrosis

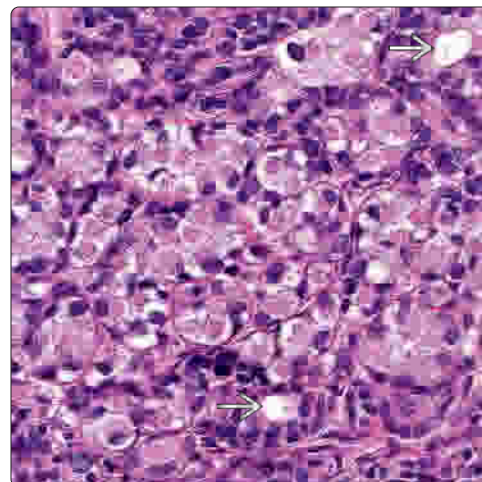




(Left) The ductal, luminal cells may have an oncocytic appearance in a few tumors. The biphasic appearance is still appreciated in this tumor, with the darker nuclei of the myoepithelial cells present at the periphery of the tubules. Immunohistochemistry would help to highlight this separation. **(Right)** In a solid area like this, only isolated tubules are present . The luminal cells have an oncocytic or granular cytoplasm. The myoepithelial cells appear more basaloid in this field.

Oncocytic Variant of EMC

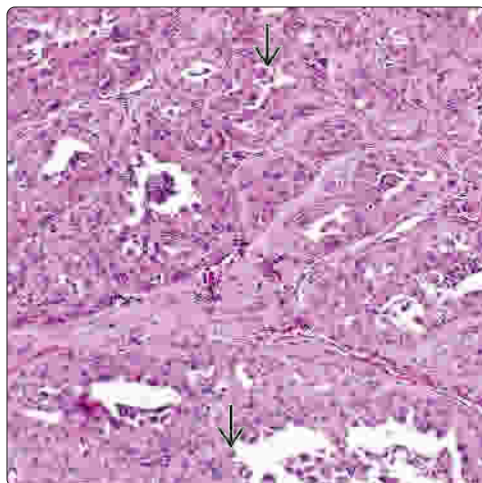


Oncocytic Variant of EMC

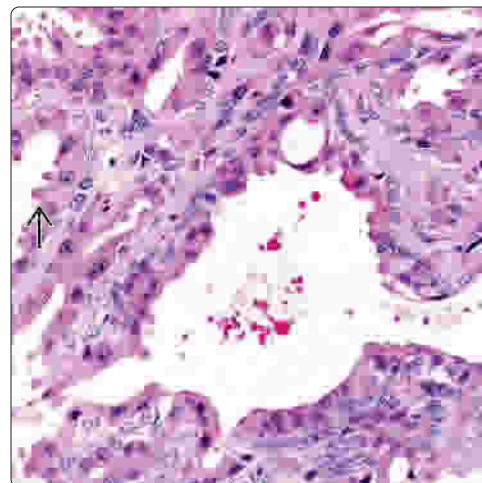


(Left) Apocrine ductal components with snouts or decapitation secretions are noted  in this apocrine EMC variant. Focal cribriform features can be seen in this still biphasic tumor. **(Right)** The inner luminal cell compartment shows an apocrine appearance, with brightly eosinophilic cytoplasm and cytoplasmic snouting. There is decapitation secretions . Note the increased pleomorphism in the luminal cells.

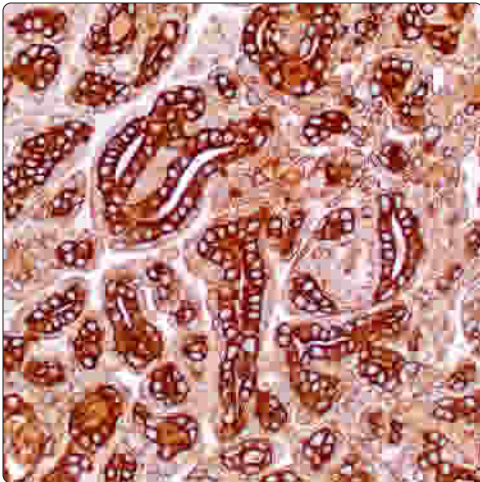
Apocrine Variant of EMC



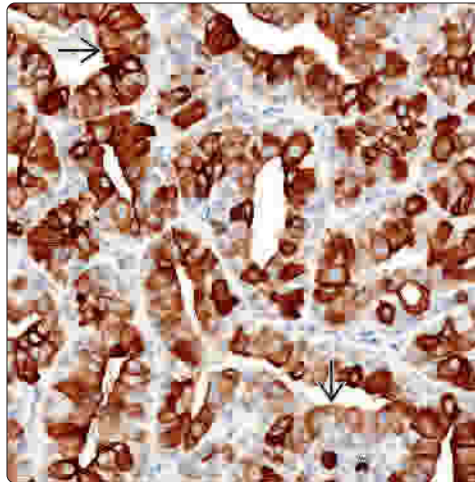
Apocrine Variant of EMC



Biphasic CK-PAN Reactivity

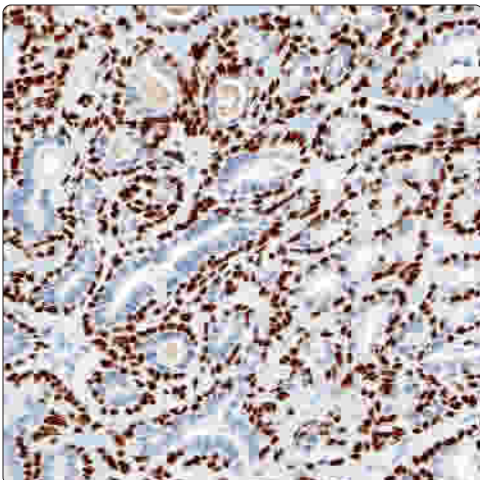


CK7 Highlights Luminal Cells

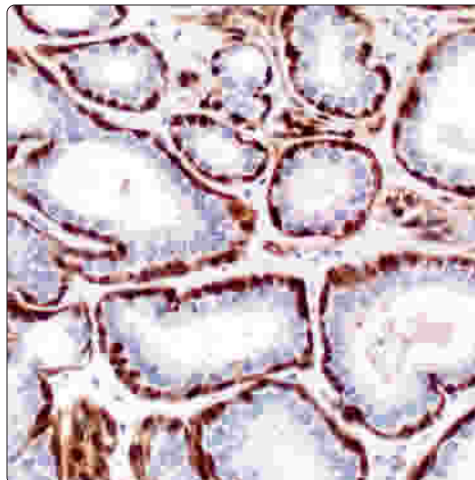


(Left) Both the epithelial and myoepithelial cells are highlighted with pan-keratin. However, there is an accentuation with a darker reactivity of the ductal-luminal cells than the myoepithelial cells. (Right) In many tumors, the keratin (in this case, CK7) highlights only the ductal-tubule inner luminal cells. This type of staining helps to reinforce the histologic duality of this neoplasm.

Myoepithelial p63 Reaction

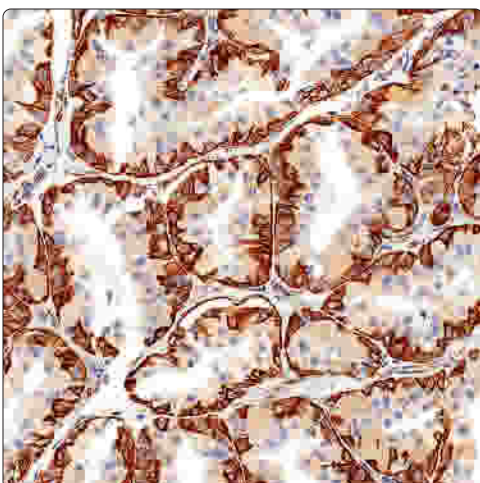


S100 Protein Basal Reaction

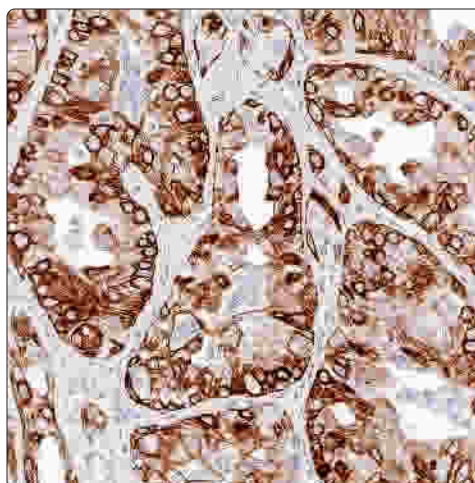


(Left) p63 strongly and diffusely highlights the nuclei of neoplastic myoepithelial cells in this EMC. Note that the inner luminal/ductal cells are not stained with this marker. Of course, p63 is immunoreactive in many salivary gland neoplasms. (Right) Strong, nuclear and cytoplasmic reaction in the basal-myoeplithelial cell compartment with S100 protein is shown. This biphasic appearance is characteristic.

Abluminal Actin Reactivity



Strong Basal CK5/6 Reaction



(Left) Myoepithelial cells react with a variety of immunohistochemistry studies, although the smooth muscle actin often gives the most characteristic and strong reactivity. Calponin, muscle-specific actin, and CK14 give a similar result. (Right) Basal-myoeplithelial cells are highlighted with CK5/6. This apocrine type EMC shows focal reactivity in the luminal cells also.

Adenocarcinoma, Not Otherwise Specified

KEY FACTS

TERMINOLOGY

- Salivary gland carcinoma with ductal differentiation that lacks distinctive features of other salivary gland cancers

CLINICAL ISSUES

- Variable incidence, based on extent of testing
- Most common in parotid gland
- Usually asymptomatic
- Complete excision is primary treatment, approach depends on tumor
- Majority in major glands (parotid specifically)
- Minor glands accounts for ~40% of cases
- Depending on reporting, may represent 3rd most common malignant salivary gland tumor
- Wide age range, peak in 6th-7th decades

MACROSCOPIC

- Irregular invasive margins

MICROSCOPIC

- May have very small areas characteristic of specific salivary gland tumor
- Grade reflects cytologic atypia

TOP DIFFERENTIAL DIAGNOSES

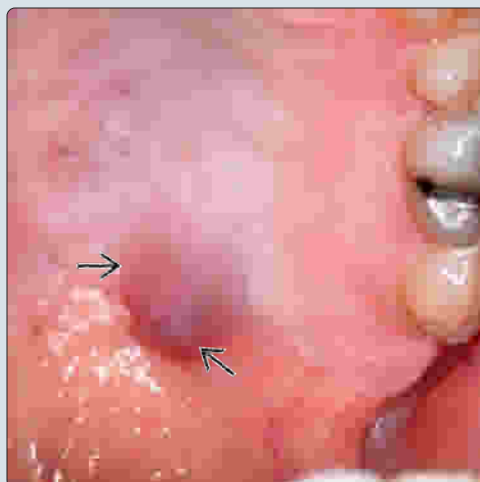
- Diagnosis of exclusion

GRADING

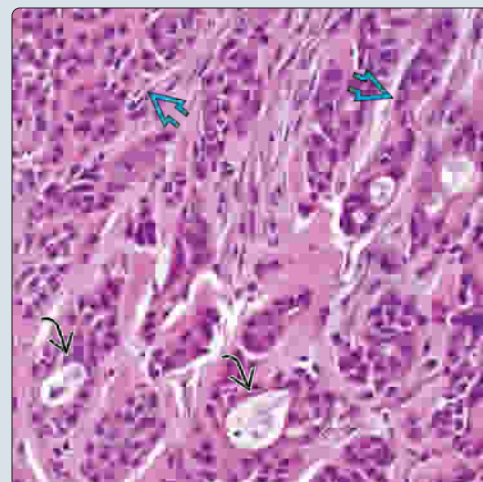
- Separated into 3 grades based on degree of ductal/tubular differentiation, pleomorphism, and mitoses
- Grade 1:** Well-formed ductal/tubular structures; mild pleomorphism; small nucleoli; few mitoses
- Grade 2:** Less ductal/tubular structures; moderate pleomorphism; increased mitoses
- Grade 3:** Limited ductal/tubular structures (sufficient to diagnose adenocarcinoma); moderate to severe pleomorphism; hyperchromasia; increased mitoses, including atypical forms; necrosis and hemorrhage

Palatal Adenocarcinoma, NOS

(Left) While the majority of adenocarcinoma, not otherwise specified (NOS) tumors occur in the major glands, this tumor affected the palate. The patient had no complaints of pain and stated the mass had been noticed over a year prior to it being identified on a routine dental exam. (Right) This tumor was diagnosed as adenocarcinoma, (NOS). It shows tubular and ductal structures, while it lacks any of the specific features of other salivary gland neoplasms.

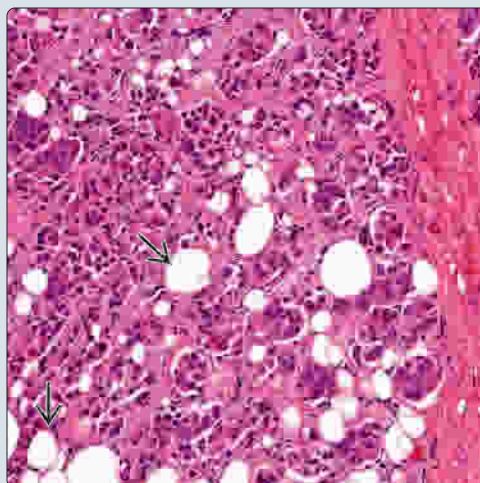


Tubular and Ductal Structures

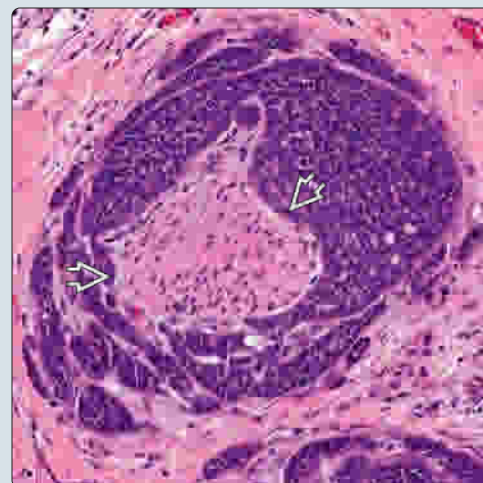


Islands of Tumor Within Fat

(Left) Hematoxylin and eosin shows a tumor with closely apposed organoid islands. Cells within the islands show features of malignancy: Pleomorphism, hyperchromasia, and conspicuous nucleoli. The tumor cells are noted to invade the fat adjacent to the involved salivary gland. (Right) Hematoxylin and eosin shows a focus of perineural invasion. This is often a feature of a high-grade tumor. Other features of high-grade tumors include increased mitoses, necrosis, and hemorrhage.



Perineural Invasion of Adenocarcinoma



TERMINOLOGY

Abbreviations

- Adenocarcinoma, not otherwise specified (NOS)

Definitions

- Malignant salivary gland neoplasm with ductal differentiation that lacks distinctive histologic features of other salivary gland carcinomas

CLINICAL ISSUES

Epidemiology

- Incidence
 - Depending on reporting, variable incidence
 - Decreasing as immunohistochemistry and molecular techniques define more tumors
 - Inconsistent reporting and selection criteria limits results
- Age
 - Wide age range; peak in 6th-7th decades
- Sex
 - Females slightly more common than males

Site

- Majority in major glands (parotid specifically)
- Minor glands accounts for ~ 40% of cases
 - Hard palate, buccal mucosa, lips

Presentation

- Solitary, asymptomatic mass
- Pain (20% of patients)
 - More often in submandibular gland tumors
- Facial weakness (20% of patients)
- Minor salivary gland tumors may show ulceration
- Palate tumors may destroy bone (up to 25%)
- Wide range for duration of symptoms (up to 10 years)

Treatment

- Surgical approaches
 - Complete excision is primary treatment, approach depends on tumor location
- Adjuvant therapy
 - Postoperative radiotherapy may be indicated for intermediate to high-grade tumors

Prognosis

- Difficult to predict, due to limited studies
- Clinical stage, site of involvement, and tumor grade all influence prognosis
- **Site**
 - Intraoral tumors have better prognosis
 - Major gland tumors show decreased survival
- **Tumor grade**
 - Low-grade tumors: Longer time periods without disease, fewer distant metastases, no change in overall survival, however
 - High-grade tumors: Recurrences develop more commonly, more likely to have distant metastases

MACROSCOPIC

General Features

- Focally or partially circumscribed

- Irregular and ill-defined invasive edges
- Cut surface: Yellow-white, may have necrosis and hemorrhage

MICROSCOPIC

Histologic Features

- Diagnosis of exclusion
- Variety of patterns of growth
 - Nests, islands, cords, tubules, solid sheets
 - Ducts: Much more common in low- to intermediate-grade tumors
 - Cysts may sometimes be present
 - Presence of ducts helps in separation from other tumor types
- Neoplastic epithelium: Cuboidal to oval to columnar cells, distinct cell borders, occasional clear cells, occasional oncocytes
- Cells display variable pleomorphism, mitotic figures, and nucleoli
- Stroma can be collagenized or myxoid
- Eosinophilic, extracellular matrix, or extracellular mucin may be present
- Tumors usually invasive: Perineural and lymphovascular invasion
- May have necrosis and hemorrhage
- May have very small areas characteristic of specific salivary gland tumor

DIFFERENTIAL DIAGNOSIS

Other Salivary Gland Tumors

- Adenocarcinoma, NOS is diagnosis of exclusion

Metastatic Disease

- History of other malignancy
- Immunohistochemistry helps to confirm specific sites of origin

GRADING

Reflected by Cytologic Atypia

- Separated into 3 grades based on degree of ductal/tubular differentiation, pleomorphism, and mitoses
 - **Grade 1:** Well-formed ductal/tubular structures; mild pleomorphism; small nucleoli; few mitoses
 - **Grade 2:** Less ductal/tubular structures; moderate pleomorphism; increased mitoses
 - **Grade 3:** Limited ductal/tubular structures (sufficient to diagnose adenocarcinoma); moderate to severe pleomorphism; hyperchromasia; increased mitoses, including atypical forms; necrosis and hemorrhage

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3. Li J et al: Salivary adenocarcinoma, not otherwise specified: a collection of orphans. *Arch Pathol Lab Med.* 128(12):1385-94, 2004
4. Ihrler S et al: Differential diagnosis of salivary acinic cell carcinoma and adenocarcinoma (NOS). A comparison of (immuno-)histochemical markers. *Pathol Res Pract.* 198(12):777-83, 2002

Clear Cell Carcinoma

KEY FACTS

TERMINOLOGY

- Epithelial malignant salivary gland neoplasm characterized by proliferation of clear cells set within loose to densely hyalinized stroma

CLINICAL ISSUES

- Minor salivary glands predominate (~ 80%)
- ~ 25% have regional nodal metastasis at presentation
- Base of tongue, palate, floor of mouth, buccal mucosa, lip, and tonsillar area (in descending order)

MICROSCOPIC

- Infiltrative mass composed of sheets, cords, nests, or trabeculae of monotonous epithelial cells with variably clear cytoplasm
- Stroma loose and myxoid to dense and hyalinized
- Rare mitotic activity
- Perineural invasion in about 1/2 of cases

ANCILLARY TESTS

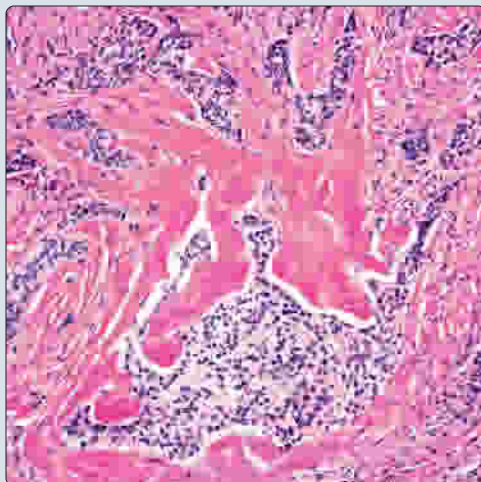
- **Positive:** CCC & HCCC: Low molecular weight cytokeratins, pan-cytokeratins, CEA
 - HCCC: p63 and high molecular weight cytokeratin
 - CCC: Typically p63 **negative**
- **Negative:** S100 protein, actin-sm, muscle-specific actin, myosin, calponin, GFAP, CK20
- HCCC: *EWSR1* (22q12) translocation
- CCC: Absence of *EWSR1* (22q12) translocation

TOP DIFFERENTIAL DIAGNOSES

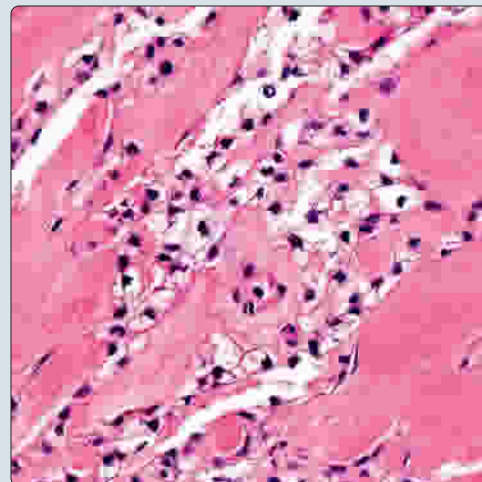
- **Salivary gland neoplasms with clear cells**
 - Mucoepidermoid carcinoma, epithelial-myoepithelial carcinoma, acinic cell carcinoma, myoepithelial carcinoma, oncocytoma, myoepithelioma
 - No *EWSR1* rearrangement
- **Metastatic renal cell carcinoma**
 - IHC coexpression of keratin and vimentin, with CD10, pax-2, and anti-renal cell carcinoma reactivity

Hyalinizing Clear Cell Carcinoma

(Left) The typical appearance of hyalinizing clear cell carcinoma (HCCC) is composed of clear cells arranged in cords and nests within a heavily hyalinized stroma. (Right) A high-power magnification of clear cell carcinoma displays cords and trabeculae of epithelial cells with clear cytoplasm, set within a densely collagenized, acellular stroma. The neoplastic cells have monomorphic, basophilic crinkled nuclei. Mitotic figures are rare.

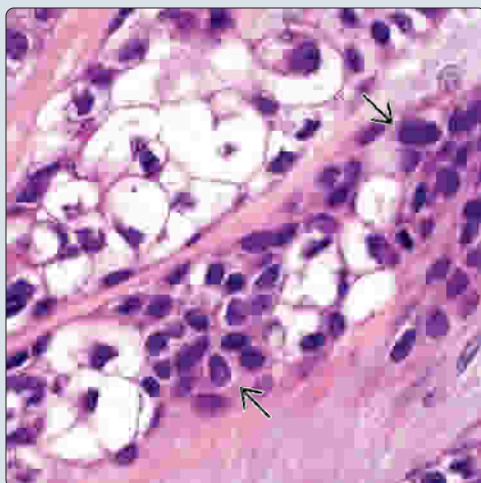
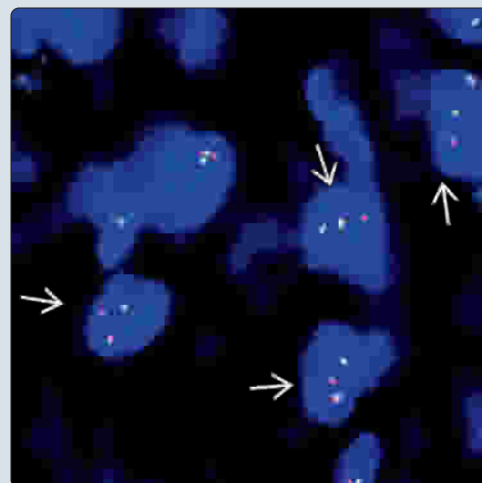


HCCC With Irregular Basophilic Nuclei



Clear and Eosinophilic Cells in HCCC

(Left) At high-power magnification, 2 cell types are evident; the epithelial cells are round to polygonal with well-defined cytoplasmic borders [B]. Intracytoplasmic glycogen accumulation accounts for cell expansion and clear cell change. (Right) Fluorescence in situ hybridization dual-color break-apart probe demonstrates the presence of *EWSR1* rearrangement in HCCC [B]. There is 1 normal fused signal (yellow) and 1 each of the split spectrum green and spectrum orange signals. This does not confirm the fusion partner.

*EWSR1* Rearrangement

TERMINOLOGY

Abbreviations

- Clear cell carcinoma (CCC)

Synonyms

- Glycogen-rich CCC

Definitions

- CCC is low-grade malignant salivary gland carcinoma composed of cells with clear cytoplasm lacking features of other clear cell-rich salivary gland carcinomas
- Hyalinizing CCC (HCCC) is distinctive salivary gland carcinoma of epithelial differentiation with hyalinized stroma and characteristic *EWSR1-ATF1* gene fusion
 - Based on differences in IHC and molecular findings, HCCC postulated to be variant of squamous cell carcinoma

ETIOLOGY/PATHOGENESIS

Cell of Origin

- HCCC: Glandular (ductal) or squamous derivation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare (< 1% of all salivary gland tumors)
- Age
 - Mean: 6th decade; range: 24-78 years
- Sex
 - HCCC: Male < female (1:1.2)

Site

- Minor salivary glands predominate (~ 80%)
 - Base of tongue, palate, floor of mouth, buccal mucosa, lip, and tonsillar area (in descending order)
 - Any minor salivary gland site may be affected
- Minority in major glands
 - Parotid >> submandibular gland
- Also reported in parotid, larynx, nasopharynx, and hypopharynx

Presentation

- Swelling or mass lesion
 - Dome-shaped or sessile
 - Possible mucosal surface ulceration
- May erode or extend into underlying bone
- Occasional association with pain
 - Additional symptomatology varies by location
 - Dysphonia, dysphagia, bleeding, or obstruction
- Duration of symptoms: 1 month to 15 years
 - Typically show slow growth
- ~ 25% have regional nodal metastasis at presentation
 - Minority may have distant metastases to lung or bone

Treatment

- Surgical approaches
 - Wide surgical excision with clear margins
 - Selective neck dissection should be considered due to propensity for local nodal spread
- Adjuvant therapy

- Pending adequacy of excision and presence of metastases

Prognosis

- Excellent survival
 - ~ 20% recurrence rate
- Virtually no patients die from disease
- Long-term follow-up due to possibility of recurrence and regional nodal metastasis

IMAGING

Radiographic Findings

- Submucosal mass at hard-soft palate junction
- Hard palate erosion and greater palatine foramen enlargement

MR Findings

- Best imaging modality; less affected by dental amalgam
- Signal intensity similar to muscle
- Excellent contrast differentiation between neoplasm and surrounding fat
- T2WI: High signal compared with muscle
- Perineural growth highlighted

MACROSCOPIC

General Features

- Poorly circumscribed, infiltrating into adjacent tissues
- Cut surface is grayish-white
- Cystic change uncommon
- Prominent hyalinization imparting scar-like appearance

Size

- Mean: 2 cm (most < 3 cm)

MICROSCOPIC

Histologic Features

- Infiltrative mass composed of sheets, cords, nests, or trabeculae of monotonous epithelial cells with variably clear cytoplasm
 - Majority of cells round to polygonal with eccentric nuclei with well-defined cell borders
 - Minority of cells are relatively small with eosinophilic cytoplasm
 - May be admixed or at periphery of clear cell nests
 - May also form small groups or islands
 - Glandular duct formation typically absent
 - Rare mitotic activity
 - Perineural invasion in about 1/2 of cases
 - Focal necrosis, associated with risk of recurrence
 - Focal squamous differentiation or squamous pearls
 - Nearly 1/2 of HCCCs show mucinous differentiation
 - Both focal intracellular mucin and more diffuse mucinous differentiation
- HCCC: Frequent connection to surface epithelium
 - Pagetoid extension of HCCC into epithelium
 - Pseudoepitheliomatous hyperplasia
- Stroma
 - Loose and myxoid to dense and hyalinized
 - Dense hyalinization most common

Cytologic Features

- Aspirates contain cohesive groups/sheets of small and large epithelial cells with sharp outlines
- Uniform round to ovoid nuclei, granular chromatin, and small nucleoli
- Well-defined clear cytoplasm

ANCILLARY TESTS

Histochemistry

- Clear cells reactive with PAS and diastase sensitive
 - Indicating intracytoplasmic glycogen accumulation
- HCCC: Mucicarmine positive in ~50% of cases

Immunohistochemistry

- **Positive:** CCC and HCCC: Low molecular weight cytokeratin, pan-cytokeratins, CEA
 - **HCCC:** p63 and high molecular weight cytokeratin positive; **CCC:** Typically p63 **negative**
 - Stroma positive for collagen IV and laminin around tumor nests
- **Negative:** S100 protein, actin-sm, muscle-specific actin, myosin, calponin, GFAP, CK20

Electron Microscopy

- **HCCC:** Tight junctions and desmosomes
 - Tonofilaments and microvilli
 - Basal lamina usually identified

Fluorescence In Situ Hybridization

- **HCCC:** *EWSR1* (22q12) translocation

DIFFERENTIAL DIAGNOSIS

Salivary Gland Neoplasms With Clear Cells

- **Malignant**
 - Mucoepidermoid carcinoma, epithelial-myoepithelial carcinoma, acinic cell carcinoma, myoepithelial carcinoma
 - Conventional and oncocytic mucoepidermoid carcinomas usually show *MAML2* rearrangement
 - HCCC does not have cysts lined by goblet cells, whereas mucoepidermoid carcinoma does not exhibit sclerosis and cord-like growth pattern of HCCC
 - Other tumors usually show characteristic pattern somewhere in sample, often with different immunohistochemistry profile
- **Benign:** Oncocytoma, myoepithelioma, pleomorphic adenoma
- No *EWSR1* rearrangement

Metastatic Renal Cell Carcinoma

- Prominent sinusoidal vessels, hemorrhage, and IHC coexpression of keratin and vimentin, with CD10, pax-2, CAIX, and anti-renal cell carcinoma (RCC) reactivity, favoring renal primary
- No *EWSR1* rearrangement

Clear Cell Odontogenic Carcinoma

- Rare malignant tumor arising in jaws of dental lamina origin
- *EWSR1* (22q12) translocation present in 83% of cases
- May be considered odontogenic analog of HCCC
- Can be difficult to distinguish from HCCCs that erode and invade adjacent bone

Calcifying Epithelial Odontogenic Tumor, Pindborg Tumor

- May have clear cell component
- **Positive** for stromal amyloid (Congo red; IHC)
- No *EWSR1* rearrangement

Squamous Cell Carcinoma

- May see sclerosis and infiltrative epithelial cords of tumor cells similar to HCCC
- Nuclear pleomorphism, mitotic figures, and surface dysplasia are not features of HCCC
- No *EWSR1* rearrangement

DIAGNOSTIC CHECKLIST

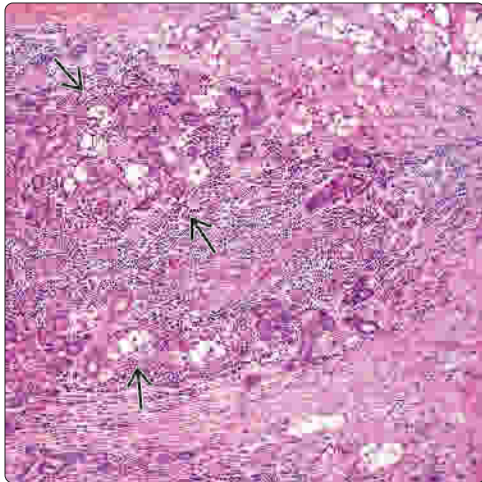
Pathologic Interpretation Pearls

- When diagnosis is not readily apparent, FISH analysis for *EWSR1* should be done

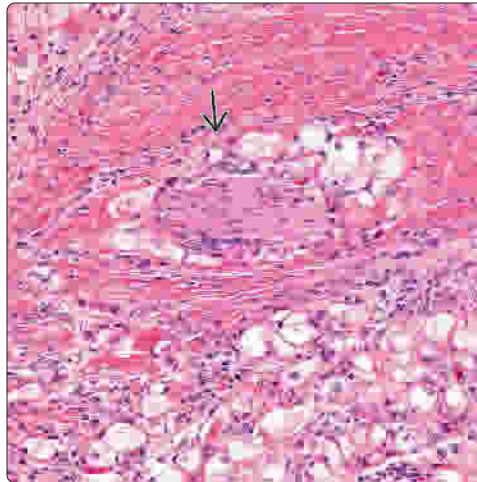
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Clear Cell Carcinoma With Infiltrative Growth Pattern

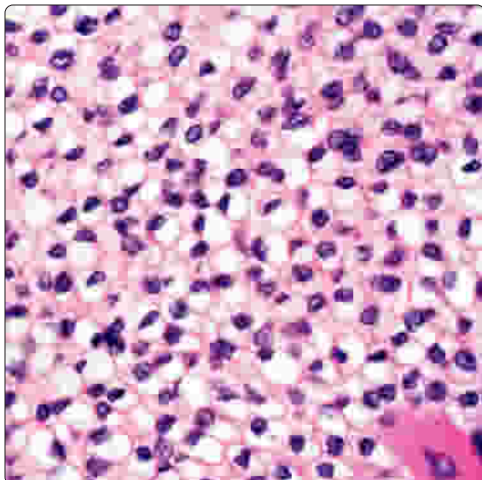


Perineural Invasion in Clear Cell Carcinoma

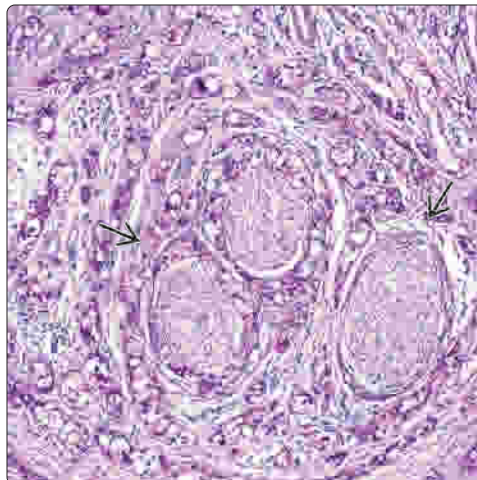


(Left) Both CCC and HCCC often exhibit an infiltrative growth pattern, as illustrated here. Tumor cells are seen extending into the minor salivary glands. In some cases, HCCC may be well delineated. When arising in minor salivary glands, the overlying epithelium can exhibit pseudoepitheliomatous hyperplasia. (Right) Perineural invasion can be seen in about 50% of CCC and HCCC; however, angiolymphatic invasion is a rare finding, as are necrosis and mitoses.

Clear Cell Carcinoma

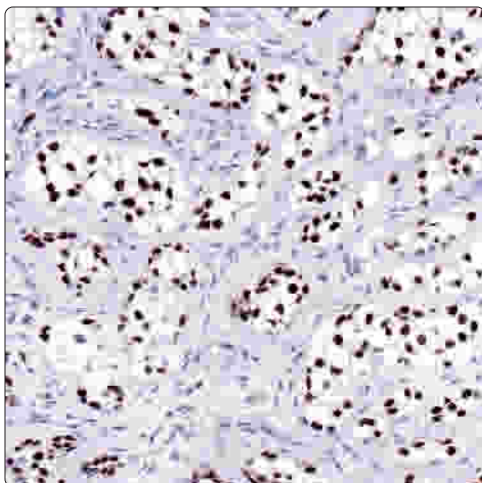


PAS Positivity in Clear Cell Carcinoma

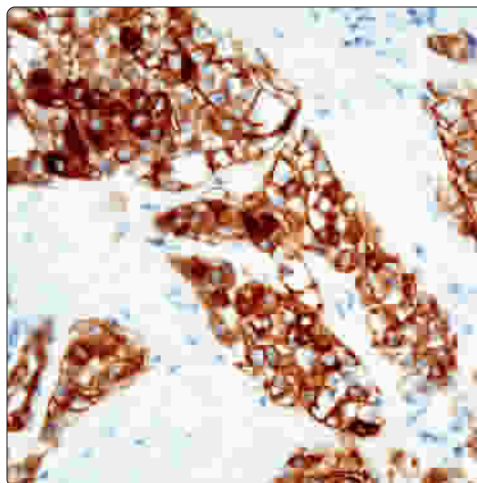


(Left) Tumor cells can grow as sheets of clear cells. The clear cells may show occasional mucin positivity, which does not preclude the diagnosis of CCC. Unlike HCCC, CCC is p63 negative and does not have the EWSR1-ATF1 gene fusion. (Right) The clear cells of CCC show granular PAS(+) material, which is diastase sensitive, confirming the presence of cytoplasmic glycogen. Perineural invasion is highlighted in this image.

p63 Positivity in HCCC



Keratin Positivity in HCCC



(Left) HCCCs show strong nuclear immunoreactivity for p63 but lack staining with S100 protein, actins, glial fibrillary acidic protein, and vimentin. This immunoprofile helps to differentiate HCCCs from other clear cell neoplasms, including epithelial-myoepithelial carcinoma. (Right) HCCCs are immunoreactive for high molecular weight cytokeratin markers as illustrated by the strong and diffuse AE1/AE3 cytoplasmic staining.

Cystadenocarcinoma

KEY FACTS

TERMINOLOGY

- Malignant epithelial salivary gland neoplasm characterized by predominantly cystic growth with intraluminal papillae

CLINICAL ISSUES

- Mean: 6th decade; range: 20-86 years
- Slowly growing (mean: 4 years), painless swelling or compressible mass
- Parotid: ~ 70%; minor salivary glands: ~ 25%
- Complete wide surgical excision yields excellent prognosis: ~ 100% 5-year survival

MACROSCOPIC

- Partially circumscribed but unencapsulated

MICROSCOPIC

- Partially circumscribed with prominent cystic appearance
 - Cysts may be back to back or show limited fibrous connective tissue stroma
 - Duct-like structures may be part of cystic appearance

- Papillary growth is almost always present
 - Papillae vary from single simple projections with delicate fibrovascular cores to complex, arborizing structures filling the lumen
- Cysts and papillae lined by bland, small and large cuboidal to columnar cells with vacuolated cytoplasm
- Tumor-associated lymphoid proliferation is frequently present
- Rare dystrophic calcification or psammoma-like bodies
- Mitoses are infrequent; necrosis is uncommon

ANCILLARY TESTS

- **Positive:** Pancytokeratin, CK7, CEA-M, EMA
- **Negative:** S100 protein, AR, basal p63

TOP DIFFERENTIAL DIAGNOSES

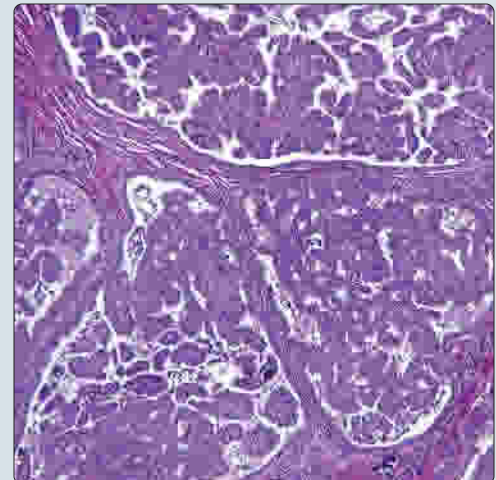
- Cystadenoma, acinic cell carcinoma (papillary-cystic type), mucoepidermoid carcinoma, salivary duct carcinoma, low-grade intraductal carcinoma

Cyst With Complex Arborizing Papillae

(Left) There is a circumscribed tumor with a large cyst filled by complex, arborizing papillary structures. Invasion is not appreciated in this field. Note the mucinous material in the cystic spaces. (Right) The predominantly cystic appearance of the tumor is separated by delicate fibrous connective tissue septa. The papillary structures are quite complex, lined by cuboidal to columnar cells.

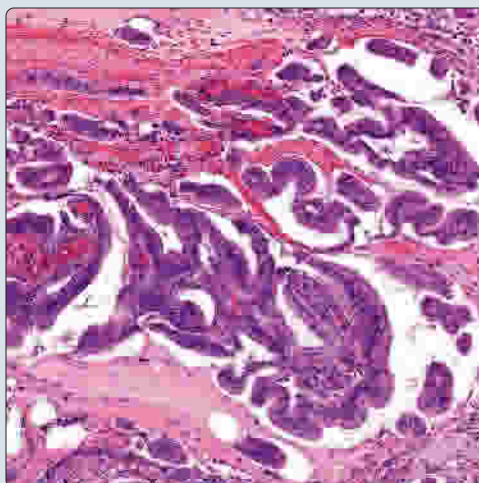


Fibrous Septa Separate Cysts

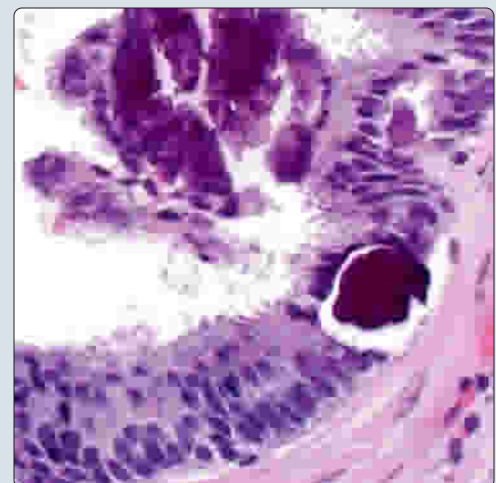


Mucinous Tumor With Pseudostratification

(Left) Neoplastic proliferation shows a number of duct-like structures and papillae suspended in a mucinous background. The cells lining the papillary structures are columnar, with multiple layers of cells, giving a pseudostratified appearance. (Right) The tall columnar cells show limited pleomorphism in this field, with small nucleoli noted. Dystrophic to psammoma body-like calcifications can be seen in some tumors.



Dystrophic Calcifications



TERMINOLOGY

Definitions

- Malignant epithelial salivary gland neoplasm characterized by predominantly cystic growth with intraluminal papillae
 - Lacks specific histopathologic features of other salivary carcinomas with cystic growth
 - Malignant counterpart of cystadenoma

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare (< 1%)
- Age
 - Mean: 6th decade; range: 20-86 years

Site

- Parotid is most commonly affected (~ 70%)
- Minor salivary glands (~ 25%)
 - Order of frequency: Buccal mucosa, lips, palate, floor of mouth, tongue, retromolar region

Presentation

- Slowly growing, painless swelling or compressible mass
 - Symptoms present for long duration (mean: 4 years)
- Palate tumors may erode bone

Treatment

- Complete wide surgical excision

Prognosis

- Excellent prognosis (low grade): ~ 100% 5-year survival
- Recurrences are uncommon (~ 10%), years after primary
- Lymph node metastases are uncommon (~ 10%)

MACROSCOPIC

General Features

- Partially circumscribed but unencapsulated
- Multicystic, often filled with fluid or mucin

Size

- Range: 0.4-6 cm

MICROSCOPIC

Histologic Features

- Well circumscribed but not usually encapsulated
- Limited invasion into parenchyma, soft tissue, nerves, &/or vessels
 - Invading islands may be solid
 - Cysts may appear quite a distance from main tumor mass
- Prominent cystic appearance
 - Haphazard cysts, sometimes filled with mucin
 - Cysts may be back to back or show limited fibrous connective tissue stroma
 - Duct-like structures may be part of cystic appearance
 - Relatively few, large cysts may be seen
 - Rare dystrophic calcification or psammoma-like bodies
- Papillary growth is nearly always present
 - Single, simple projections with delicate fibrovascular cores to complex, arborizing structures

- Cysts and papillae lined by small and large cuboidal to columnar cells
 - Can be mucinous, clear, or oncocytic (rare)
 - Multiple cell layers including cribriform pattern
 - Lacks well-developed myoepithelial layer
- Cells are cytologically bland with vacuolated cytoplasm
- Mitotic figures are usually infrequent
- Tumor-associated lymphoid proliferation is frequently present
- Necrosis is uncommon
- Lacks squamous or transitional appearance

ANCILLARY TESTS

Cytology

- Fluid (mucinous) background with inflammatory cells
- Variable cellularity with small number of cohesive tumor cell clusters and micropapillae
- Tumor cells are bland, small to medium, possibly showing overlapping, eccentric round nuclei

Immunohistochemistry

- **Positive:** Pancytokeratin, CK7, CEA-M, EMA
- **Negative:** S100 protein, AR, basal p63

DIFFERENTIAL DIAGNOSIS

Cystadenoma

- Frequently unencapsulated, lacking invasion; no atypia; multicystic appearance does not equate with invasion

Acinic Cell Carcinoma, Papillary-Cystic Type

- Microcystic growth with papillae lined by vacuolated small cells, often with pigment in cytoplasm
- Solid areas with larger cells showing acinar cells with basophilic, granular cytoplasm

Low-Grade Intraductal Carcinoma

- Large, usually unilocular cyst with ramifying smaller cysts; lined by tufted papillae to Roman bridge architecture; apocrine snouts; low to intermediate nuclear grade
- **Positive:** S100 protein; pancytokeratin; p63 (basal layer); often androgen receptor; sometimes mammaglobin

Salivary Duct Carcinoma

- Cystic appearance may be prominent; large pleomorphic cells; abundant cytoplasm; mitoses; necrosis
- **Positive:** AR; **negative:** p63, CK5/6, S100 protein



Mucoepidermoid Carcinoma

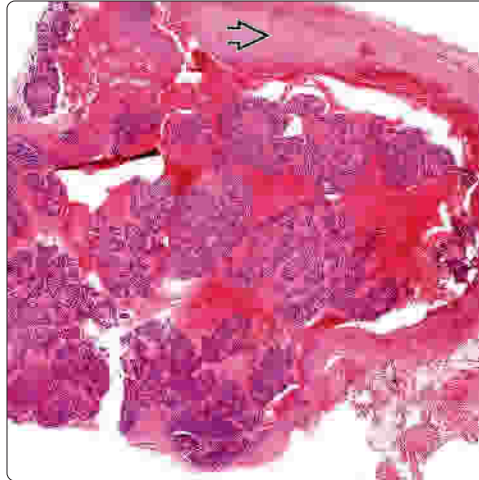
- Cystic appearance is characteristic (low-grade tumors), although solid areas can predominate
- 3 cell types: Mucocytes, intermediate, and epidermoid cells

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Circumscribed Tumor With Papillae

(Left) Fibrous connective tissue may be seen at the periphery , but a well-formed capsule with smooth muscle-walled vessels is usually absent. The epithelial proliferation is arranged in complex and arborizing to pencil-like papillary projections. **(Right)** There is an infiltration of the epithelial groups into the surrounding parenchyma and soft tissue below the surface epithelium . Cystic spaces are present, but this lesion shows a slightly more solid appearance. The papillae are lined by columnar cells.

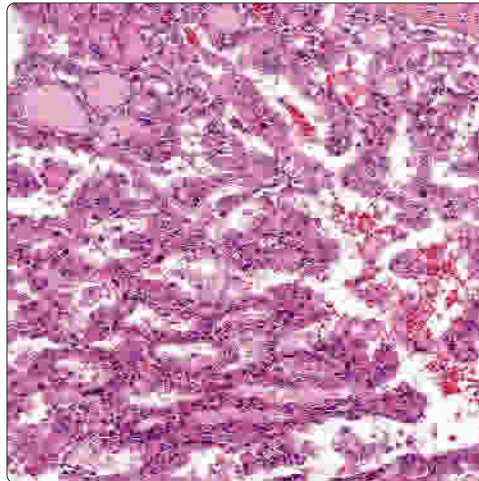


Subepithelial Cystic Papillary Neoplasm

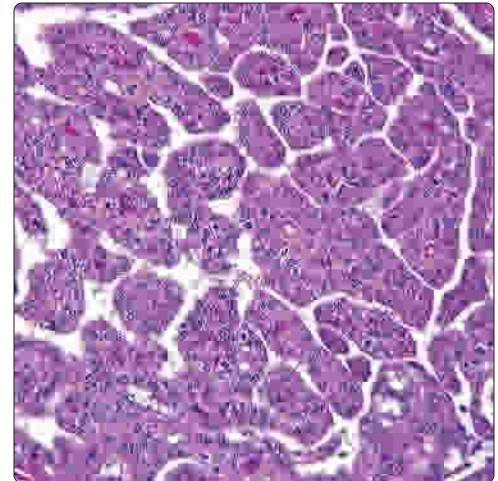


Complex Papillary Structures

(Left) This tumor shows a significantly complex papillary architecture, confirmed by free-floating papillae. The cells lining the spaces are cuboidal to low columnar, showing a vacuolated, bubbly cytoplasm. The differential diagnosis includes an acinic cell carcinoma, papillary-cystic variant. **(Right)** There is a more stout or thick appearance to the papillae in this case. However, the columnar cells lining the papillae show cuboidal cells with limited to absent cytologic atypia.

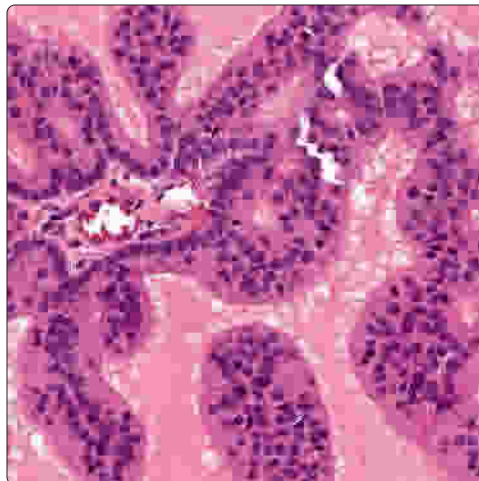


Stout Papillae

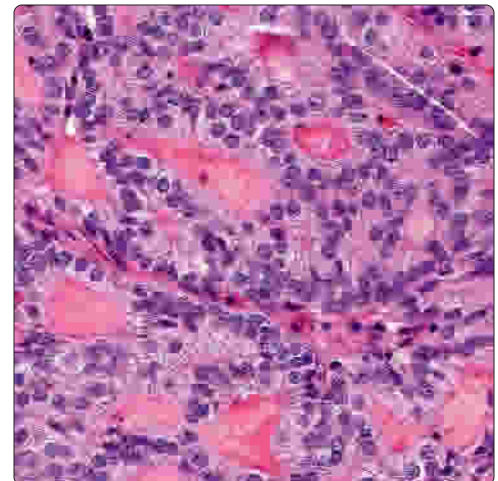


Bland Cuboidal to Columnar Lining Cells

(Left) High-power magnification shows cuboidal to columnar epithelial cells with slightly eosinophilic cytoplasm and basally located round and regular nuclei. **(Right)** These cytologically bland cells show the glandular appearance or duct-like appearance that can be seen in cystadenocarcinoma. The cytoplasm is slightly vacuolated to soap bubble in appearance. Nucleoli are small and inconspicuous. Mitoses are not seen.



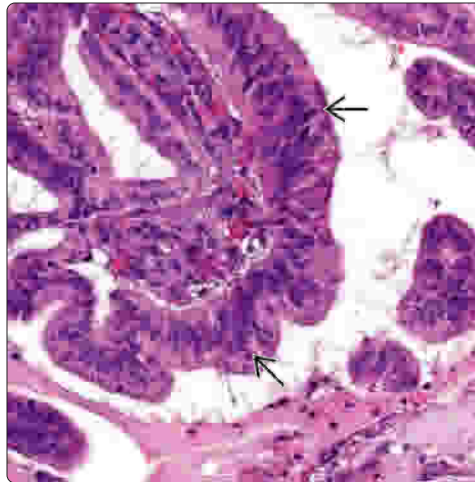
Ductal Differentiation



Simple Papillae With Calcifications

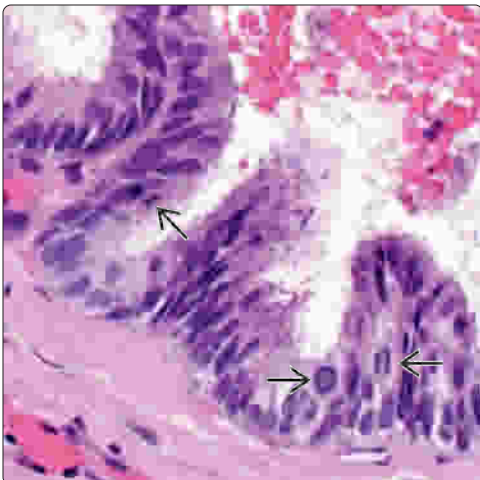


Nuclear Stratification



(Left) There is mucinous material within a large cystic space lined by columnar cells with delicate, simple papillary structures projecting into the lumen. Calcifications are noted [1]. (Right) A stratified nuclear appearance [2] is quite prominent in this papillary structure. However, the nuclei are quite bland. There is a vague mucinous quality to the cystic material.

Mitoses May Be Seen

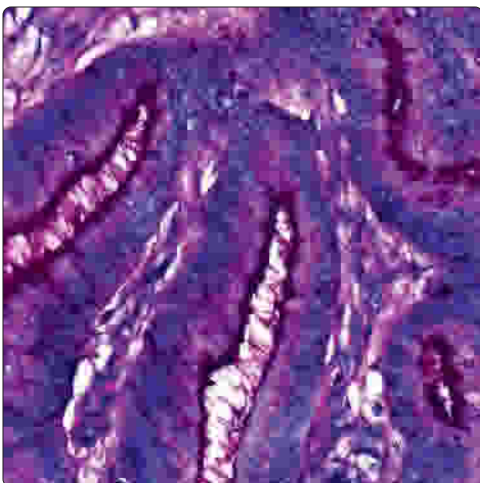


Mucinous Material at Luminal Surface

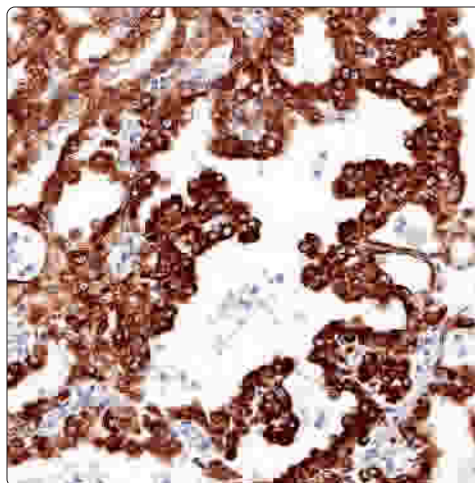


(Left) A pseudopapillary tufting is noted in this tumor, which shows several mitoses [1]. Increased mitotic figures are uncommon in this tumor type. (Right) A mucicarmine stain highlights a luminal mucinous material [2], which is also noted within the apical cytoplasm of a few of the cells [3]. The mucinous material can be highlighted with mucicarmine or with PAS, although, it is uncommon to have a strong reaction.

Mucinous Material Highlighted With PAS



CK7 Highlights Epithelial Cells



(Left) The PAS/diastase stain can be used to highlight the intracellular and extracellular mucinous material. Small cytoplasmic granules along with accentuation at the luminal border is characteristic. (Right) Immunohistochemistry studies can help with the differential diagnosis. CK7 (shown), pancytokeratin, EMA, and CEA are positive to a variable degree in these tumors. However, S100 protein and AR are negative.

Myoepithelial Carcinoma

KEY FACTS

TERMINOLOGY

- Malignant tumor of exclusively myoepithelial differentiation
- Malignant counterpart to myoepithelioma

CLINICAL ISSUES

- Uncommon; most occur in parotid gland
- Wide age range
- Usually present with rapidly expanding, painless mass
 - Multiple recurrences of pleomorphic adenoma or myoepithelioma is risk factor
- Complete resection; chemoradiation shows mixed results
- Recurrences are common (~ 1/3), frequently multiple times

MACROSCOPIC

- Most unencapsulated
- Nodular

MICROSCOPIC





- Variable patterns of growth
- Invasive growth
- Myoepithelial cells: Plasmacytoid, epithelioid, or spindled, showing pleomorphism
- Mucoïd or myxoid stroma
- May be carcinoma of carcinoma expleomorphic adenoma
- No ducts identified

ANCILLARY TESTS

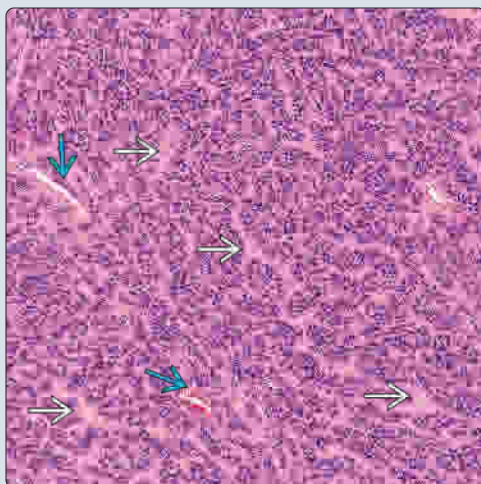
- Combinations of IHCs most useful, although limited
- **Positive:** CK5/6, S100 protein, actins, GFAP, vimentin

TOP DIFFERENTIAL DIAGNOSES

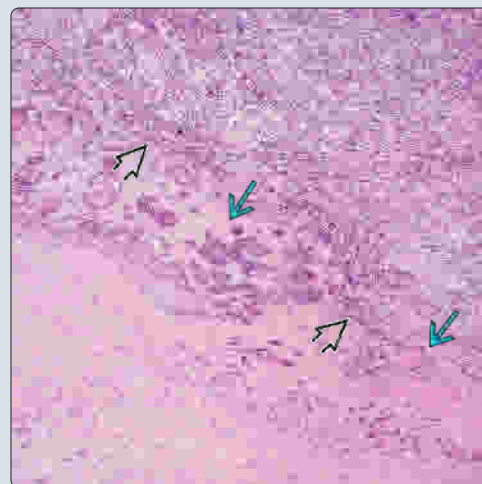
- Myoepithelioma
- Sarcomas
- Epithelial-myoepithelial carcinoma
- Plasmacytoma



(Left) There are a number of patterns of growth in this myoepithelial carcinoma. There is a prominent eosinophilic basal lamina  surrounding many of the tumor nests/islands. Ducts are not present; however, vascular channels  are readily seen in this tumor. **(Right)** This image shows a myoepithelial carcinoma  arising from a pleomorphic adenoma (PA) . The patient, a 44-year-old man, had a 6-year history of a mass in the parotid gland that recently started to enlarge.

Prominent Basal Lamina

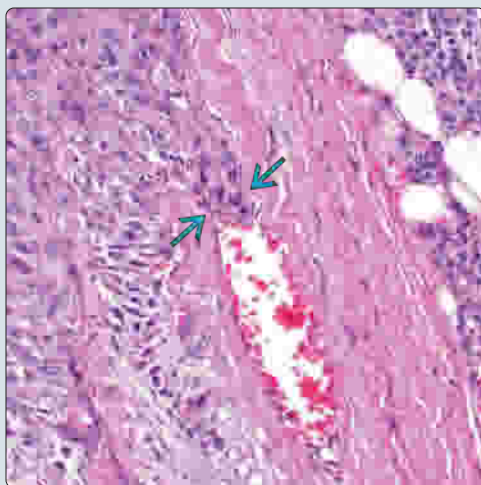


Myoepithelial Carcinoma Arising From Pleomorphic Adenoma

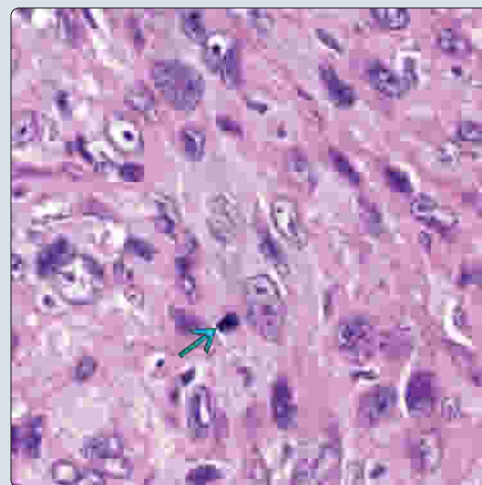


(Left) Myoepithelial carcinomas have an invasive growth pattern, helpful when considering other entities in the differential diagnosis. In this image, lymphovascular invasion  is readily identified. **(Right)** Mitotic figures  are generally easily identified, including atypical forms. In this particular field, marked pleomorphism is seen. However, in other areas, this particular tumor appeared cytologically bland.

Lymphovascular Invasion



Mitotic Figures and Pleomorphism



TERMINOLOGY

Synonyms

- Malignant myoepithelioma

Definitions

- Malignant tumor of exclusively myoepithelial differentiation
- Malignant counterpart to myoepithelioma

ETIOLOGY/PATHOGENESIS

Pathogenesis

- ~ 50% of myoepithelial carcinomas develop within preexisting pleomorphic adenoma or from myoepithelioma

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon
 - < 2% of malignant salivary gland neoplasms
 - Likely to be underreported
 - Included in World Health Organization classification in 1991
- Age
 - Wide range
 - Mean: 6th decade
 - Rare in children
- Sex
 - Equal gender distribution

Site

- Most occur in parotid gland (~ 75%)
- Submandibular gland and minor salivary glands less commonly affected

Presentation

- Usually presents with rapidly expanding, painless mass
- Tumors tend to be locally destructive
- Occasionally will be painful or tender
- Dysphagia uncommon
- Weight loss can be seen

Natural History

- Some patients report rapid increase in previous benign tumor (like pleomorphic adenoma)
- Multiple recurrences of pleomorphic adenoma or myoepithelioma is risk factor

Treatment

- Surgical approaches
 - Complete resection
 - Major glands: Parotidectomy or submandibulectomy
 - Minor glands: Wide local excision
- Adjuvant therapy
 - Chemotherapy and radiation yield mixed, debatable results

Prognosis

- Tumors may be locally aggressive
- Regarded as intermediate- to high-grade tumor
 - ~ 1/3 of patients die of disease

- Marked cellular pleomorphism and high proliferation index suggest worse clinical outcome

- Recurrences are common (~ 1/3), frequently multiple times
- Regional and distant metastases are uncommon at presentation but may occur later in disease
- Cervical metastases before distant metastases
 - Lung and other sites
- Clinical outcome may be worse for those tumors arising from pleomorphic adenoma or myoepithelioma

IMAGING

Radiographic Findings

- Bone destruction is most often seen in minor salivary gland disease

MACROSCOPIC

General Features

- Most tumors are unencapsulated, but are usually well defined
- Nodular or bosselated surface
- Gray-white, firm, glassy cut surface
- Cystic degeneration and necrosis are uncommon

Size

- Range: 2-10 cm

MICROSCOPIC

Histologic Features

- Invasive growth
 - Most helpful feature in separation from benign tumor
 - Adjacent bone may be involved
 - Perineural and lymphovascular invasion frequent
- Patterns
 - Nodular to diffuse
 - Tumor cells arranged in nests, sheets, or cords
 - Usually highly cellular, but hypocellular lesions can be seen
- Ducts are not present (by definition)
- Myoepithelial cells
 - Range from plasmacytoid to epithelioid to spindled, in various combinations
 - Marked pleomorphism can be seen but is usually limited
 - Cytoplasm can be clear
- Stroma
 - Muroid or myxoid
 - Due to accumulation of proteoglycans
 - Basal lamina can be present
 - Cartilaginous tissue is rare
- Mitotic figures are usually easy to find, including atypical forms
- Necrosis is uncommon
 - May be associated with biopsy or FNA
- May be malignant component within carcinoma ex-pleomorphic adenoma
 - Pleomorphic adenoma (PA) may include ducts
- Rare squamous differentiation

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
Vimentin	Positive	Cytoplasmic	Strong and diffuse
S100	Positive	Nuclear & cytoplasmic	Usually strong and diffuse in all neoplastic cells
Calponin	Positive	Cytoplasmic	Not as frequently positive as S100 protein
CK-PAN	Positive	Cytoplasmic	Usually majority of cells are positive
SMHC	Positive	Cytoplasmic	Variable intensity
Actin-sm	Positive	Cytoplasmic	
CK7	Positive	Cytoplasmic	Variable expression
CK5/6	Positive	Cytoplasmic	
GFAP	Positive	Cytoplasmic	Usually highlights only isolated cells
CK14	Equivocal	Cytoplasmic	Variable expression

ANCILLARY TESTS

Cytology

- Features are diverse and may lack characteristics of malignancy
- Cells are arranged in small clusters
- Cells appear epithelioid, plasmacytoid, spindled, or clear
 - Frequently mixture of cell types

Immunohistochemistry

- Nonneoplastic myoepithelial cells will react with many of same antigens
- Generally of limited practical use
 - Exception is in separation from sarcoma
- Combinations or limited panels are most useful
 - **Positive:** CK5/6, S100 protein, GFAP, vimentin

Genetic Testing

- Up to 50% may have aberrations
 - Chromosome 8 alterations are most frequently identified
- *EWSR1* rearrangements, more common in clear cell variants, are associated with poor clinical outcome

Electron Microscopy

- May demonstrate
 - Actin filaments, pinocytotic vesicles, desmosomes, and basal lamina
 - Longitudinally oriented 6-8 nm cytoplasmic microfilaments with focal dense bodies
- Infrequently utilized for diagnostic purposes

DIFFERENTIAL DIAGNOSIS

Myoepithelioma

- Lacks infiltrative growth and cytologic atypia
- Identical immunohistochemical findings

Sarcomas

- Synovial sarcoma
 - Biphasic type has glandular structures, but may be challenge with monophasic type
 - Distinctive chromosomal translocation t(X;18)
 - **Positive:** TLE1; **negative:** GFAP
- Leiomyosarcoma

- Cellular tumor comprised of interlacing fascicles
- Perinuclear cytoplasmic clearing adjacent to cigar-shaped nuclei
 - **Negative:** S100 protein, GFAP, CD117
- Rhabdomyosarcoma
 - More common in children
 - Often more pleomorphism; high mitotic rate; strap cells; plasmacytoid cells
 - **Positive:** Desmin, myogenin, myoglobin, MYOD1

Epithelial-Myoepithelial Carcinoma

- Numerous ducts
 - Lumen lined by eosinophilic, cuboidal duct cells
 - Duct cells surrounded by large polygonal clear myoepithelial cells
- Usually shows biphasic pattern with immunohistochemistry

Plasmacytoma

- Plasmacytoid cells with clock face nuclear chromatin distribution
- Perinuclear hof, or clearing, is characteristic
- **Positive:** CD138, CD79a, with κ or λ restriction
- **Negative:** S100 protein, GFAP, actins, and smooth muscle myosin heavy chain (SM-MHC)

DIAGNOSTIC CHECKLIST

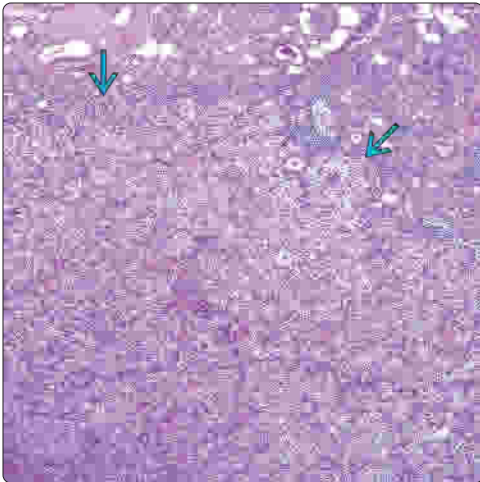
Pathologic Interpretation Pearls

- Diagnosis requires interpretation of tumor morphology and immunohistochemistry

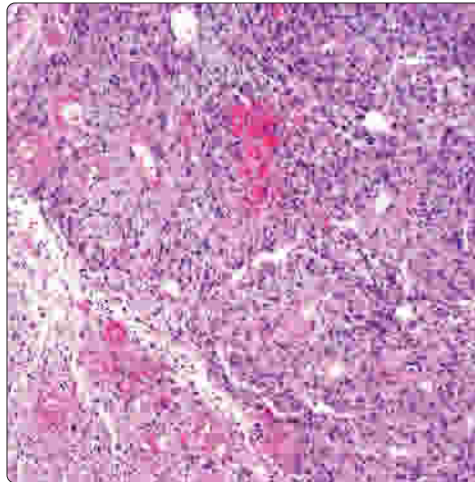
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Clear Cells in Myoepithelial Carcinoma

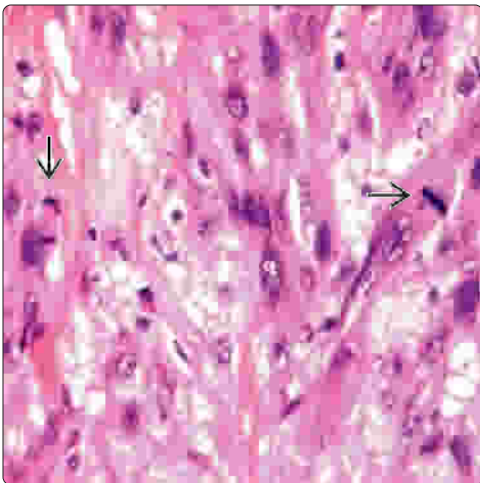


Metastatic Tumor in Lung

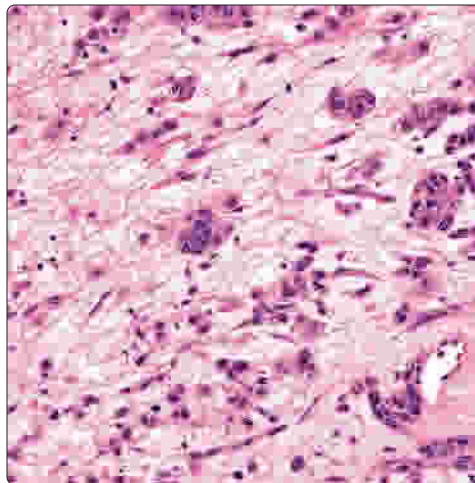



(Left) Hematoxylin & eosin shows a low-power view of a predominately clear cell tumor. The tumor lacks a well-defined capsule but is seen invading into the native salivary gland . Other clear cell salivary gland tumors should be considered in the differential diagnosis. **(Right)** This patient had multiple local recurrences of myoepithelial carcinoma and eventually presented with nodules in the lung, seen here. The patient died of this disease within months.

Mitotic Figures

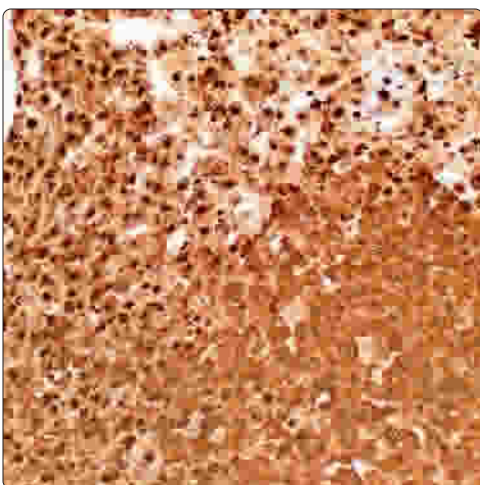


Myxoid Stroma

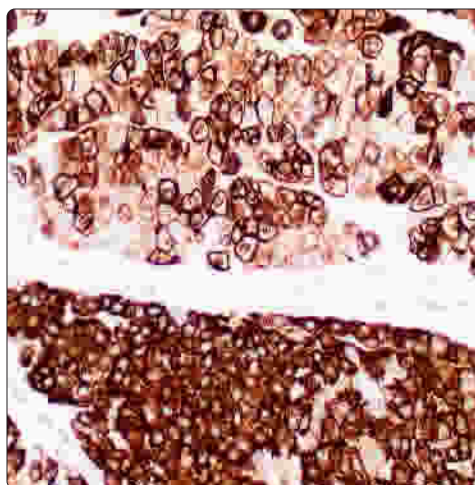


(Left) This tumor shows pleomorphism and atypical mitotic figures. Mitoses , including atypical forms, are common and reflect the intermediate- to high-grade behavior of these tumors. Note how this histological appearance could bring up the differential diagnoses of a sarcoma. **(Right)** This tumor shows a myxoid stroma instead of a hyalinized appearance. The cells have a haphazard distribution. The cells are epithelioid, although focally a suggestion of plasmacytoid features is noted.

Strong Diffuse S100 Protein Reaction



Variable CK7 Immunoreactivity



(Left) The neoplastic cells of a myoepithelial carcinoma will usually show a strong and diffuse reaction with S100 protein, as shown here. It is both a cytoplasmic and nuclear reaction. **(Right)** This myoepithelial carcinoma shows a variable reaction with CK7, strong and diffuse in the lower field, and more accentuating the cell membranes in the upper field.

Small Cell Undifferentiated Carcinoma

KEY FACTS

TERMINOLOGY

- Malignant epithelial neoplasm characterized by small, undifferentiated cells with scant cytoplasm, fine nuclear chromatin, and inconspicuous nucleoli
 - Demonstrates neuroendocrine differentiation

CLINICAL ISSUES

- Male > female (2.4:1)
- Vast majority affect parotid gland (~ 80%)
- Painless, rapidly growing, firm mass
 - Cervical lymphadenopathy is common
- Combination aggressive management yields best outcome
- Highly aggressive tumor with poor overall long-term prognosis

MICROSCOPIC

- Extensive infiltration
- Arranged in solid sheets, nests, and irregular cords

- Well-formed, small areas of crushed nuclei give dark blue appearance
- Poorly differentiated tumor cells slightly larger than lymphocytes
- Uniform cells with dense nuclear chromatin and small, inconspicuous nucleoli
- Necrosis and mitoses are frequent




ANCILLARY TESTS

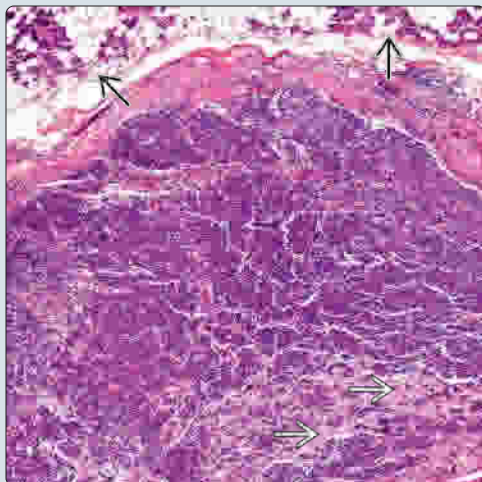
- **Positive:** CK20 perinuclear dot-like reaction; chromogranin, synaptophysin, CD56, CD57
- **Negative:** Polyomavirus (MCPyV), polyomavirus large T antigen (PVLTA)

TOP DIFFERENTIAL DIAGNOSES

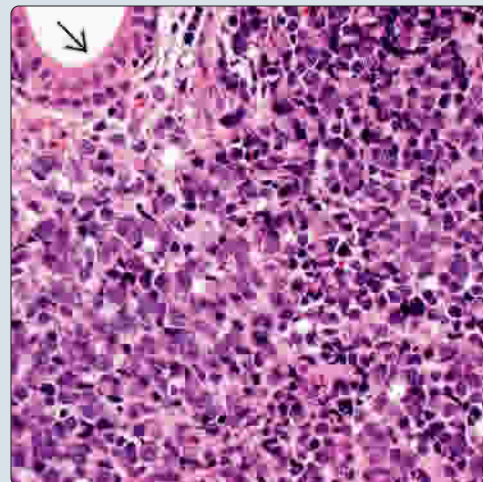
- Merkel cell carcinoma, metastatic small cell carcinoma, lymphoma, melanoma, adenoid cystic carcinoma, poorly differentiated carcinoma (squamous cell carcinoma, adenocarcinoma)

Parotid Gland Replaced by Tumor



(Left) The parotid parenchyma  is noted at the periphery. The neoplasm has a vague lobular architecture, with areas of smudged cells, characteristic of small cell undifferentiated carcinoma (SCUC). Areas of degeneration are noted . (Right) There is a small blue round cell neoplastic infiltrate adjacent to a salivary gland duct . Apoptosis and crushed nuclei are seen throughout this neoplasm. The chromatin is smudged and even.

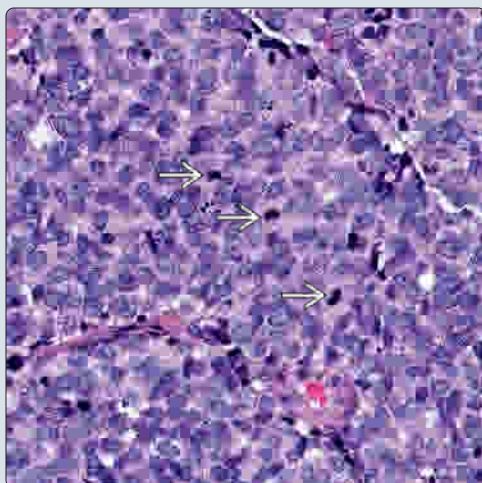


Monotonous Small Round Blue Cells

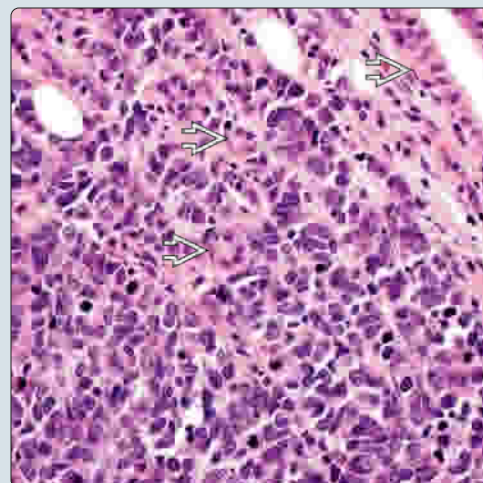


High Mitotic Index

(Left) There is a vague trabecular arrangement, with a syncytium of cells that have a very high nuclear:cytoplasmic ratio. The nuclear chromatin is even, without nucleoli. Mitotic figures are noted . (Right) The small cells have cytologic isomorphism, with apoptotic cells seen. The cells invade between the salivary gland ducts and acini . This is a characteristic pattern for this tumor type. There is some nuclear molding, with dense nuclear chromatin distribution.



Small Neoplastic Cells Adjacent to Ducts



TERMINOLOGY

Abbreviations

- Small cell undifferentiated carcinoma (SCUC)

Synonyms

- Neuroendocrine carcinoma

Definitions

- Malignant epithelial neoplasm characterized by small, undifferentiated cells with scant cytoplasm, fine nuclear chromatin, and inconspicuous nucleoli
 - Demonstrates neuroendocrine differentiation
 - Lacks histomorphologic features of either glandular or epidermoid differentiation

ETIOLOGY/PATHOGENESIS

Histogenesis

- Proposed hypothetical multipotential ductal stem cell gives rise to tumor

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare: ~ 1% of all salivary gland neoplasms
- Age
 - Wide range: 5-90 years; median: 64 years
- Sex
 - Male > female (2.4:1)

Site

- Vast majority affect parotid gland (~ 80%)
 - Submandibular gland > > intraoral minor salivary glands (buccal mucosa, tongue, tonsillar area)

Presentation

- Painless, rapidly growing, firm mass
 - Symptoms present for short duration (< 3 months)
- Fixed to adjacent tissues, including skin
- Facial nerve palsy can be seen
- Cervical lymphadenopathy is common
- Syndrome of inappropriate antidiuretic hormone production (Schwartz-Bartter syndrome) is unusual as paraneoplastic syndrome

Treatment

- Combination aggressive management yields best outcome (no individual therapy is better)
- Wide surgical excision, with ipsilateral neck dissection (in clinically positive cases)
- Chemotherapy employed for regional recurrences or distant metastases
- Postoperative radiation (up to 600 cG)

Prognosis

- Highly aggressive tumor with poor overall long-term prognosis
 - Slightly better outcome than pulmonary counterparts
- Overall 1-, 2-, and 5-year survival rates: 75.3%, 56.4%, and 36.6%, respectively
- Local recurrence develops in ~ 50% of patients

- Metastatic disease seen in > 50% of patients, usually liver, brain, and mediastinum; less frequently to lymph nodes
- Poor prognostic factors: Age ≥ 65 years, tumor size (≥ 3 cm), distant metastases, negative CK20 immunoreactivity (latter most significant)

MACROSCOPIC

General Features

- Poorly circumscribed, lobulated, infiltrating adjacent structures
- Firm, solid to fleshy, gray-white to yellow-tan, with necrosis and hemorrhage

Size

- Range: 2-10 cm; usually > 3 cm

MICROSCOPIC

Histologic Features

- Extensive infiltration
 - Adjacent parenchyma, muscle, fat, dermis, bone
 - Perineural invasion and vascular invasion are common
- Arranged in solid sheets, nests, and irregular cords
 - Cellular dyscohesion may create pseudoglandular or ductal appearance
 - Rosette formation or peripheral palisading may be seen
- Well-formed, small areas of crushed nuclei give dark blue appearance
- Abundant, dense fibrosis may separate tumor into islands or nests
 - Fibrosis may be vascularized or hyalinized
- Poorly differentiated tumor cells slightly larger than lymphocytes
 - Uniform cells with dense nuclear chromatin and small, inconspicuous nucleoli
 - Nuclear molding; scant cytoplasm, although occasionally more cytoplasm can be seen
- Coagulative &/or comedonecrosis; apoptotic bodies
- Usually high mitotic index
- Lymphoid infiltrate is limited and patchy
- Rare spindled tumor cells may be present
- Isolated areas with squamous differentiation have been reported

Variant

- Large cell type
 - Same criteria as used for large cell neuroendocrine carcinoma (LCNEC) of lung
 - Significant necrosis and high mitotic rate
 - Prominent perineural and vascular invasion
 - Large, polygonal pleomorphic cells arranged in organoid, solid, trabecular, rosette-like, and dyscohesive patterns
 - Moderate nuclear to cytoplasmic ratio, ample cytoplasm, coarse chromatin, conspicuous nucleoli
 - Cytoplasm is clear to eosinophilic
 - **Negative:** CK20

ANCILLARY TESTS

Cytology

- Cellular smears with dispersed to loose clusters of small to intermediate-sized cells

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CK-PAN	Positive	Dot positivity	Perinuclear globular or dot-like positive
CK20	Positive	Dot positivity	Perinuclear globular or dot-like positive (Merkel type)
Chromogranin-A	Positive	Cytoplasmic	Granular reactivity
Synaptophysin	Positive	Cytoplasmic	Granular reactivity
CD56	Positive	Cell membrane & cytoplasm	Most tumor cells
NSE	Positive	Cytoplasmic	Most tumor cells, but nonspecific
CD57	Positive	Cytoplasmic	Most tumor cells
CK7	Positive	Cytoplasmic	Some cases positive
EMA	Positive	Cell membrane	Most tumor cells
NFP	Positive	Cytoplasmic	Only rare and isolated tumor cells positive
Ki-67	Positive	Nuclear	> 50% tumor cells positive
Polyomavirus large T antigen	Negative		Isolated case reports of possible reactivity with polyomavirus
S100	Negative		
HMB-45	Negative		
TTF-1	Equivocal	Nuclear	Up to 20% of cells may be positive in some cases

- Mild to moderate pleomorphism, scant cytoplasm, and nuclear molding, with smudged nuclei
- Rosettes or pseudorosettes may be noted
- Multinucleated tumor cells or macrophages are uncommon

Immunohistochemistry

- CK20 perinuclear dot-like reaction is most sensitive and specific reaction
 - Present in skin Merkel cell carcinoma & primary small cell neuroendocrine carcinoma, Merkel cell type, also
 - Not seen in other salivary gland tumors nor in pulmonary small cell carcinoma
- **Positive:** Neuroendocrine markers chromogranin, synaptophysin, CD56, CD57, NSE, NFP
- **Negative:** Polyomavirus (MCPyV), polyomavirus large T antigen (PVLTA)

Genetic Testing

- Only isolated cases studied, with markedly reduced expressions of p21Waf1 and p27Kip1
- Loss of heterozygosity at chromosome 9p21 has been reported for large cell type

DIFFERENTIAL DIAGNOSIS

Merkel Cell Carcinoma (Skin)

- Direct extension from skin primary or metastasis to parotid/lymph nodes
- **Positive:** CK20, MCPyV, PVLTA; **negative:** TTF-1

Metastases

- Metastatic small cell carcinoma from lung to salivary gland is rare, but histologically identical
- TTF-1(+), CK20(-) favors lung primary

Lymphoma

- Tend to be sheet-like, infiltrating between glands and ducts
- No pseudoglandular spaces, duct-type structures, rosettes

- Variable necrosis and mitotic figures
- Smaller cells than SCUC, but with irregular contours, lacking molding
- **Positive** for lymphoma markers (i.e., CD45RB, CD20, CD30)

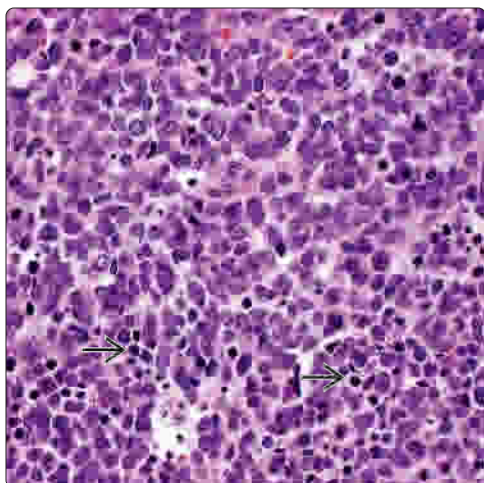
Melanoma

- Skin melanomas frequently metastasize to intraparotid lymph nodes
- Tumor cells tend to be larger, lack molding, have prominent nucleoli and intranuclear cytoplasmic inclusions
- Melanin pigment may help with separation
- **Positive:** S100, SOX10, Melan-A, HMB-45, tyrosinase

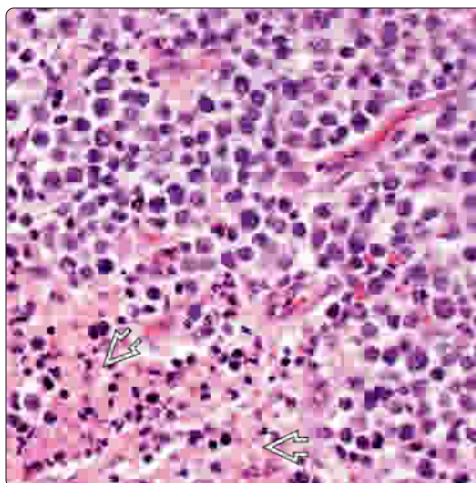
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
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Smudged Nuclei

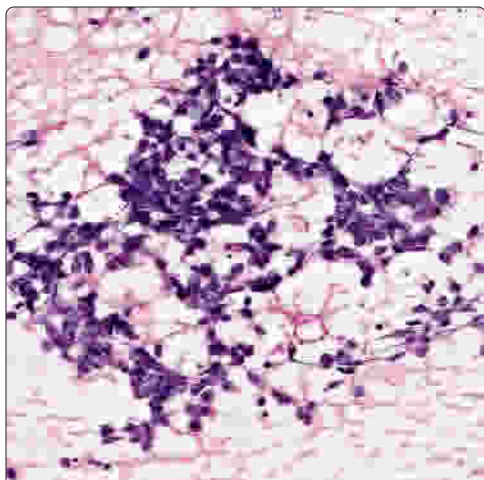


Tumor Comedonecrosis

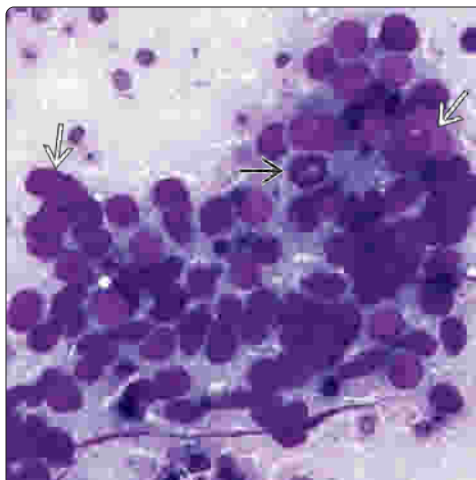




(Left) There is a sheet-like arrangement to this neoplastic proliferation of small cells with a high nuclear:cytoplasmic ratio. Numerous apoptotic bodies  are seen throughout the tumor. (Right) An area of comedonecrosis  is noted in this sheet of small neoplastic cells. These cells have scant, slightly cleared to eosinophilic cytoplasm. The chromatin is dense but even.

Nuclear Molding in FNA of Small Cell Undifferentiated Carcinoma

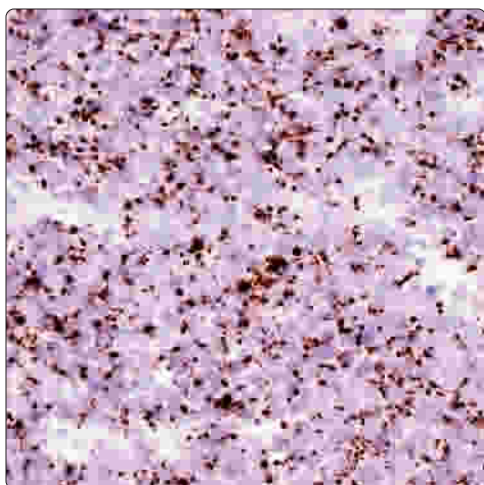


High Nuclear:Cytoplasmic Ratio

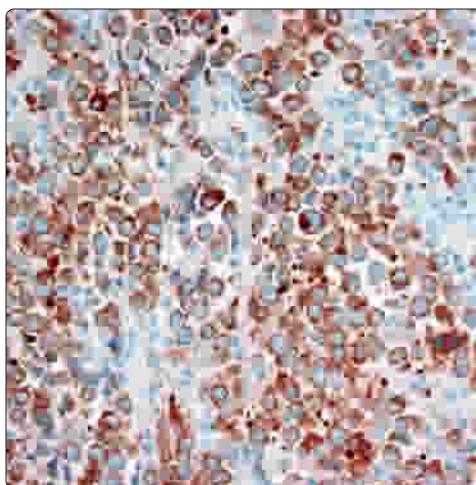


(Left) There is a cellular smear with dispersed to loose clusters of small to intermediate-sized cells. Mild pleomorphism is noted in cells that have scant cytoplasm and nuclear molding. Lymphoglandular bodies are absent. These findings on FNA can also be seen in pulmonary small cell carcinoma. (Right) There is well-developed nuclear molding  of the neoplastic cells in this FNA smear of a SCUC. There is scant cytoplasm. A mitotic figure  is noted in this small collection.

Perinuclear Dot-Like CK20 Reaction



Strong and Diffuse Synaptophysin



(Left) CK20 immunohistochemistry yields a characteristic perinuclear dot-like reaction in the cytoplasm of nearly all cells. This is one of the most sensitive and specific reactions, as it is seen neither in other salivary gland tumors nor in pulmonary small cell carcinoma. It can be seen in skin Merkel cell carcinoma, however. (Right) Nearly all of the neoplastic cells show a strong and diffuse reaction with synaptophysin in the cytoplasm of the cells. Focal "dot" or "Golgi" accentuation is seen.

Lymphoepithelial Carcinoma

KEY FACTS

TERMINOLOGY

- Undifferentiated carcinoma with associated prominent nonneoplastic lymphoplasmacytic cell infiltrate
 - Histologic features similar to nasopharyngeal carcinoma, nonkeratinizing undifferentiated type

ETIOLOGY/PATHOGENESIS

- Etiology linked to EBV
- Near 100% association in patients in endemic areas; in nonendemic areas, EBV usually absent but rarely may be identified

CLINICAL ISSUES

- Rare salivary gland tumor
- Most develop de novo but may arise in association with lymphoepithelial sialadenitis
- Predilection for Arctic region natives, Chinese, and Japanese
- Mass swelling ± pain &/or facial nerve paralysis

- Parotid gland most common site >>> submandibular gland
- High-frequency (10-40%) cervical lymphadenopathy
- Combined (multimodality) therapy treatment of choice
- 5-year survival rate reported to be 75-86%

MICROSCOPIC

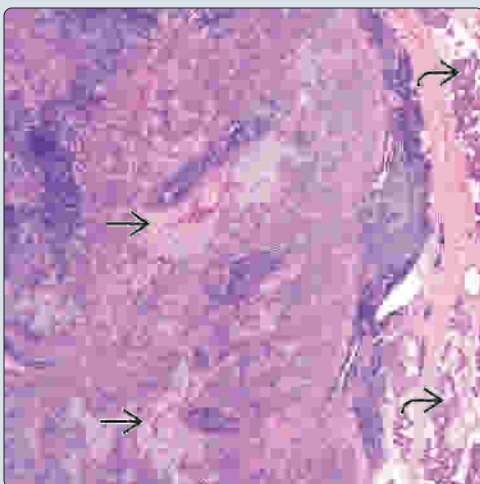
- Infiltrative tumor characterized by polygonal to spindle-shaped cells with large, round to oval, basophilic to vesicular-appearing nuclei separated or overrun by nonneoplastic lymphoid stroma
- Nonneoplastic lymphoplasmacytic cell infiltrate ± germinal centers present
- Infiltration may include into nonneoplastic salivary gland parenchyma, surrounding connective tissues, blood vessels (angioinvasion), and around nerves (neurotropism)

ANCILLARY TESTS

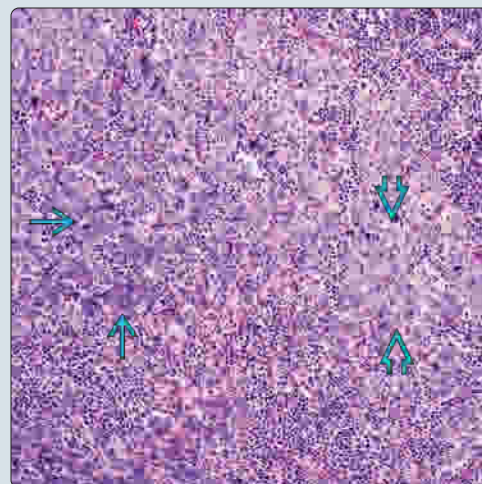
- Cytokeratins, EMA, p63 (+)
- EBER nearly always (+) (endemic cases); usually (-) but can occasionally be (+) in cases from nonendemic regions

(Left) H&E shows delineated cellular proliferation composed of lighter staining cohesive tumor nests with associated dense lymphoid proliferation that is demarcated from residual parotid gland parenchyma. **(Right)** Cohesive nests and individual cells blend into the surrounding nonneoplastic lymphocytic cell infiltrate owing to an absence of associated desmoplasia. Nevertheless, the tumor cells are readily identifiable.

Parotid Lymphoepithelial Carcinoma (LEC)

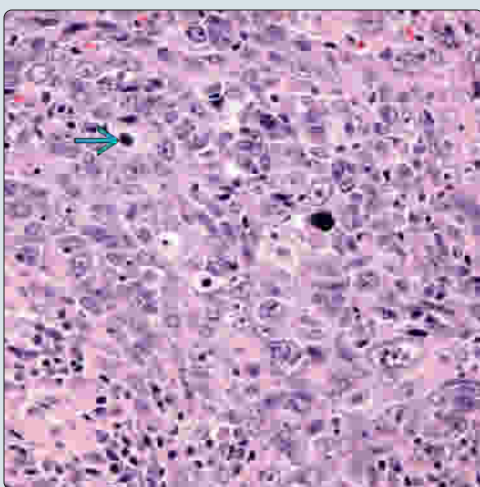


Parotid LEC

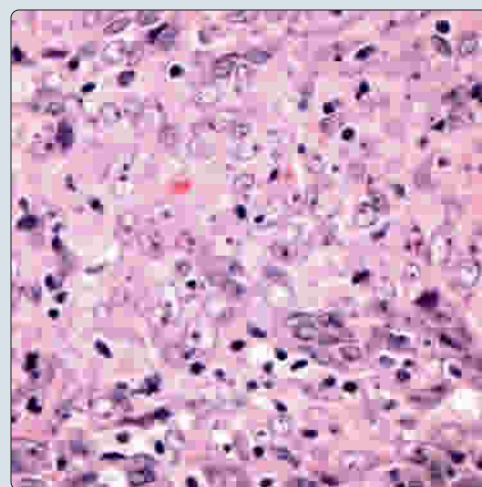


(Left) Irrespective of the setting, the neoplastic cells have enlarged vesicular nuclei with prominent nucleoli and indistinct borders. Nuclear pleomorphism and increased mitotic figures may be present. **(Right)** The neoplastic cells are characterized by enlarged nuclei with vesicular chromatin, prominent nucleoli, and indistinct borders. The dyscohesive growth and cytomorphology could be those of a large cell lymphoma, requiring immunohistochemical staining in the diagnosis and differential diagnosis.

Parotid LEC



Parotid LEC



TERMINOLOGY

Abbreviations

- Lymphoepithelial carcinoma (LEC)

Synonyms

- Undifferentiated carcinoma
- Lymphoepithelioma-like carcinoma
- Lymphoepithelial-like carcinoma
- Undifferentiated carcinoma with lymphoid stroma
- Malignant lymphoepithelial lesion
- Carcinoma ex lymphoepithelial lesion

Definitions

- Undifferentiated carcinoma with associated prominent nonneoplastic lymphoplasmacytic cell infiltrate
 - Histologic features similar to nasopharyngeal carcinoma, nonkeratinizing undifferentiated type

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Etiology linked to EBV
 - Near 100% association in patients in endemic areas
 - In nonendemic areas, EBV usually absent but rarely may be identified
 - Presence of EBV in clonal episomal form suggests role in tumor development

Familial

- Inherited trichoepitheliomas reported in setting of LEC suggesting hereditary predisposition

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare salivary gland tumor accounting for < 1% of all salivary gland tumors
 - Highest incidence worldwide in Eskimo/Inuit population
- Age
 - Occurs over wide age range with most patients in 5th decade
- Sex
 - In Eskimos/Inuits, more common in females
- Ethnicity
 - Predilection for Arctic region natives (Eskimos/Inuits from Alaska, Canada, Greenland), southeastern Chinese, and Japanese

Site

- Parotid gland most common site of occurrence (80%) followed by submandibular gland
 - Rare occurrence in minor salivary glands throughout upper aerodigestive tract

Presentation

- Mass swelling ± associated pain &/or facial nerve paralysis
 - Fixation to skin &/or underlying structures seen in advanced tumors
 - High frequency (10-40%) of concurrent cervical lymphadenopathy

Laboratory Tests

- Elevated anti-EBV viral capsid antigen IgA, anti-EBV nuclear antigen IgG in patients from endemic regions

Natural History

- Most develop de novo but may arise in association with lymphoepithelial sialadenitis
 - No known association with other autoimmune disorders
 - e.g., Sjögren disease

Treatment

- Options, risks, complications
 - Combined (multimodality) therapy treatment of choice
 - Surgical resection
 - Neck dissection
 - Radiation therapy
- Surgical approaches
 - Total parotidectomy
 - Regional neck dissection indicated given high frequency of nodal metastasis

Prognosis

- 5-year survival rate reported to be 75-86%
- Prognosis linked to clinical stage
- In Eskimos/Inuits, reported more aggressive clinical course and higher clinical stage disease at presentation

MACROSCOPIC

General Features

- Circumscribed but unencapsulated, lobulated, firm, tan-white mass

Size

- 1-10 cm in greatest dimension

MICROSCOPIC

Histologic Features

- Infiltrative tumor characterized by
 - Lobules
 - Sheets
 - Nests
 - Islands
 - Trabeculae
 - Cords of neoplastic cells separated or overrun by lymphoid stroma
- Neoplastic cells include
 - Polygonal to spindle-shaped with large, round to oval, basophilic to vesicular-appearing nuclei
 - May include spindle cells with fascicular growth
 - 1 or more prominent nucleoli
 - Abundant amphophilic to lightly eosinophilic cytoplasm
 - Cells have indistinct cell borders and syncytial growth usually evident
- Prominent basaloid morphology may be seen, referred to as basaloid LEC
 - Identified in Inuit population
 - Associated with EBV
- Moderate to marked nuclear pleomorphism present
- Increased mitotic activity and necrosis

- Nonneoplastic lymphoplasmacytic cell infiltrate \pm germinal centers present
 - Present in between and around tumor nests or may overrun and obscure epithelial component
 - Abundant histiocytes may be seen, creating starry-sky appearance
 - Noncaseating granulomatous inflammation may be identified
- Amyloid stroma may also be present
- Invasion into
 - Nonneoplastic salivary gland parenchyma
 - Surrounding connective tissues
 - Nerves (neurotropism)
 - Vessels (angioinvasion)

ANCILLARY TESTS

Cytology

- Cohesive aggregates or individual neoplastic cells include
 - Medium to large cells with large vesicular-appearing nuclei
 - 1 or more prominent nucleoli
 - High nuclear:cytoplasmic ratio
- Associated mature lymphocytes and plasma cells are typically numerous

Immunohistochemistry

- Cytokeratins, epithelial membrane antigen (EMA)
- p63 **positive** but variable reactivity may be present from case to case and even within same case
- C-kit (CD117) reactivity may be present
- p16 **negative**
- Lymphoid cells reactive for B-cell (CD20) and T-cell (CD3) markers

In Situ Hybridization

- EBV-encoded RNA (EBER) consistently positive in cases from endemic regions
 - Usually negative but can occasionally be positive in cases from nonendemic regions

DIFFERENTIAL DIAGNOSIS

Metastatic EBV-Associated Carcinoma

- Nasopharyngeal origin
- Nasopharynx
- Overlapping histologic, immunohistochemical, ultrastructural, and molecular features
- Differentiation predicated on detailed clinical evaluation to exclude primary nasopharyngeal or less commonly oropharyngeal carcinoma

Metastatic HPV-Associated Carcinoma

- Base of tongue or tonsillar origin
- Presence of p16 &/or identification of high-risk HPV by molecular testing (PCR, ISH) and absence of EBV would allow for differentiation

Malignant Lymphoma

- Hematolymphoid immunomarkers **positive**
- Epithelial immunomarkers **negative**

Large Cell (Undifferentiated) Carcinoma

- Absence of association with EBV (EBER **negative**)

Malignant Melanoma

- Melanocytic immunomarkers **positive**
 - S100 protein, HMB45, melan-A, tyrosinase, MITF1, SOX10
- Epithelial immunomarkers **negative**

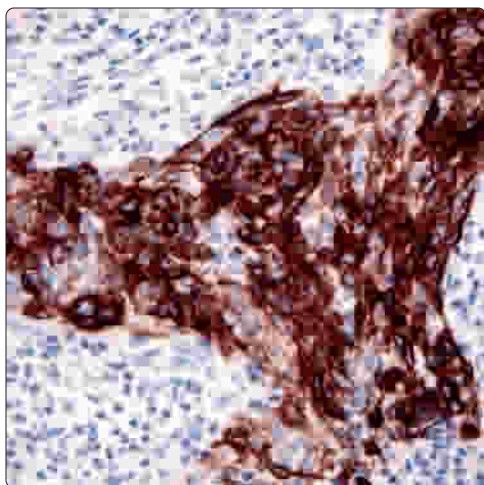
Lymphoepithelial Sialadenitis

- Characterized by
 - Presence of lymphoepithelial islands
 - Mixed inflammatory cells
 - Absence of malignant cells

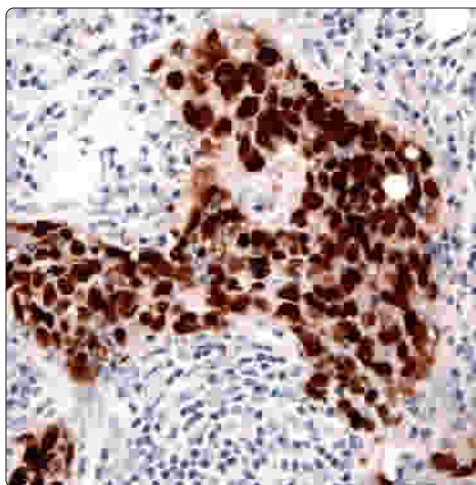
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Cytokeratin in Parotid LEC

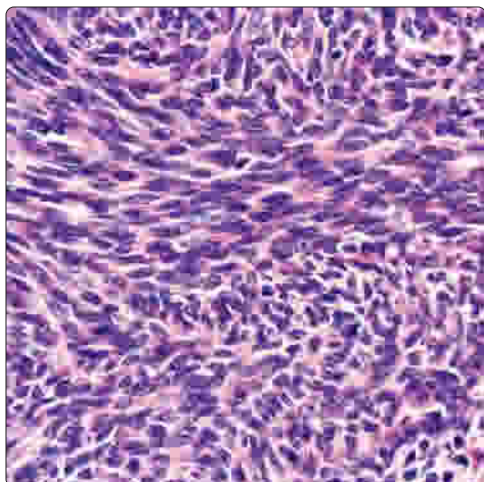


EBV-Encoded RNA in Parotid LEC

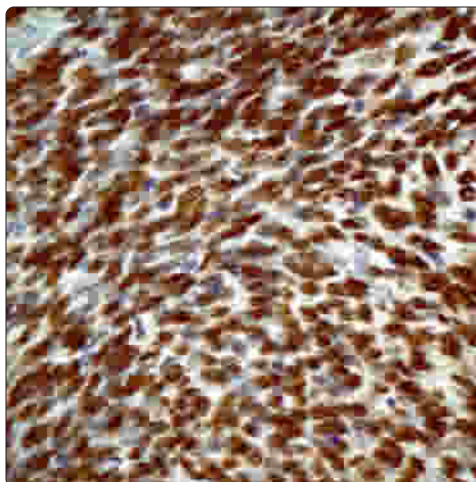


(Left) Immunohistochemical staining is essential in differentiating a salivary gland epithelial malignancy from malignant lymphoma. To this end, neoplastic cells of lymphoepithelial carcinoma are immunoreactive for a variety of epithelial markers, including diffuse and intense reactivity for pancytokeratin. **(Right)** In situ hybridization for EBV-encoded RNA (EBER) shows the neoplastic cells to be diffusely positive (nuclear staining), confirming the diagnosis of LEC.

LEC, Spindle Cell Features

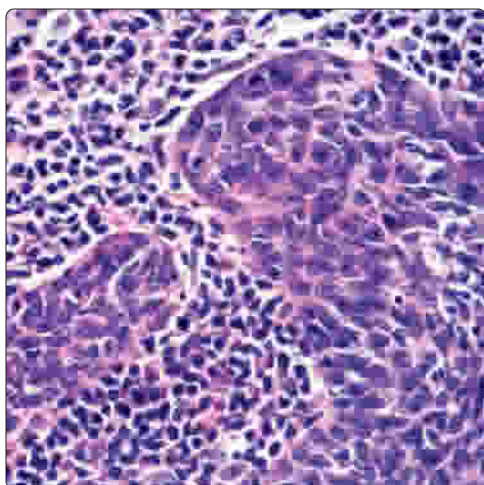


LEC, Spindle Cell Features

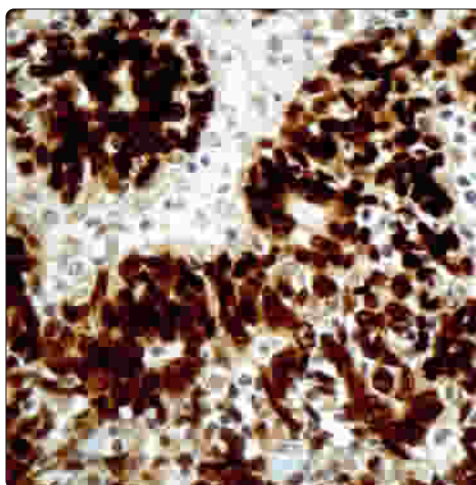


(Left) Variant histologic features in parotid gland LEC include the presence of a spindle cell neoplastic proliferation with fascicular growth. Such features may be focally present or more diffusely present in any given case. **(Right)** In situ hybridization for EBV shows the neoplastic spindle-shaped cells to be diffusely positive (nuclear staining), confirming the diagnosis of parotid gland LEC, albeit with spindle cell features.

Basaloid LEC



Basaloid LEC



(Left) A variant type of LEC is characterized by the presence of prominent basaloid cell cytomorphology (in contrast to the more usual vesicular nuclei) and is referred to as basaloid LEC. **(Right)** In situ hybridization for EBV shows the neoplastic basaloid cells to be diffusely positive (nuclear staining), confirming the diagnosis of basaloid-type LEC and differentiating it from other basaloid salivary gland neoplasms.

KEY FACTS

TERMINOLOGY

- Malignant basaloid salivary gland tumor identical to basal cell adenoma, except showing invasion and capacity for metastasis

CLINICAL ISSUES

- Mean age: 7th-8th decades
- Parotid gland most commonly affected (85-90%)
- Painless swelling, enlargement, or mass
- Considered low-grade malignant tumor, with good long-term prognosis
- May be locally destructive with recurrence

MICROSCOPIC

- Unencapsulated, circumscribed to infiltrative
- Invasion into parenchyma, fat, skeletal muscle, vessels, nerves
- Necrosis can be seen (~ 45%)
- Mitotic figures increased

- Multiple patterns of growth: Solid, membranous, tubulotrabeular
- Nests separated by eosinophilic basement membrane-like material
- **Small, dark** basaloid cells predominate
- **Large polygonal** cells
- Peripheral nuclear palisading at junction with stroma




ANCILLARY TESTS

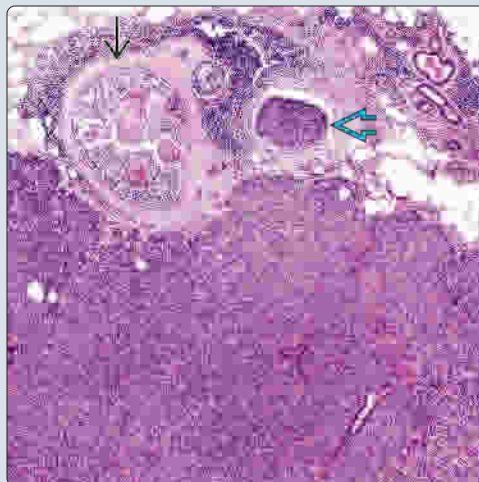
- Immunohistochemistry identifies dual differentiation
 - Ductal epithelial and myoepithelial
 - Most lack nuclear β -catenin reaction

TOP DIFFERENTIAL DIAGNOSES

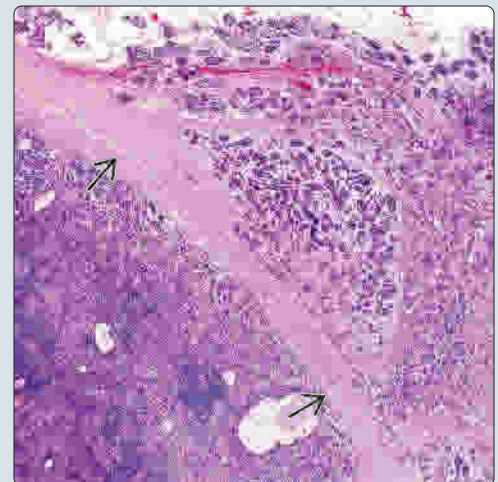
- Basal cell adenoma
- Adenoid cystic carcinoma
- Pleomorphic adenoma
- Basaloid squamous cell carcinoma
- Metastatic basal cell carcinoma

Invasion Into Soft Tissue




(Left) The basaloid neoplasm is surrounded by a very thin, irregular capsule. There are areas of extension into the adipose tissue  still associated with fibrosis. Vascular invasion  is noted in this basal cell adenocarcinoma (BCAC). **(Right)** There is a thick fibrous connective tissue capsule  containing the tumor. However, there are innumerable areas of extension out into the adjacent parotid gland parenchyma as well as into the adjacent adipose tissue.

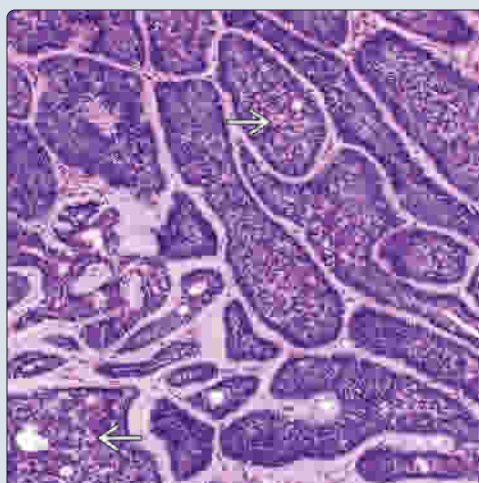


Capsular Invasion in Basal Cell Adenocarcinoma

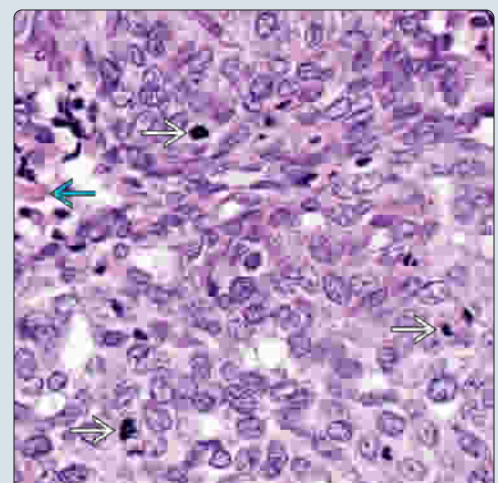


Jigsaw Basement Membrane Deposition

(Left) This image highlights the heavy deposition of collagenous septations that dissect the tumor lobules into a jigsaw appearance. There are also globules or droplets of reduplicated basement membrane material  that are quite characteristic in basal cell adenoma or BCAC. **(Right)** The basaloid cells have scant cytoplasm surrounding nuclei that have a vesicular appearance. There are numerous mitoses . Note the reduplicated basement membrane material .



Increased Mitoses in Basal Cell Adenocarcinoma



TERMINOLOGY

Synonyms

- Malignant basal cell adenoma
- Carcinoma ex monomorphic adenoma

Definitions

- Malignant basaloid salivary gland tumor identical to basal cell adenoma, except showing invasion and capacity for metastasis
 - Considered malignant counterpart of basal cell adenoma

ETIOLOGY/PATHOGENESIS

Inherited

- Autosomal dominant inherited Brooke-Spiegler syndrome
 - Multiple benign skin tumors (spiradenoma; cylindroma) with rare malignant transformation into basal cell adenocarcinoma (BCAC), among other tumor types

Precursor

- While most arise de novo, few cases develop from basal cell adenoma

Histogenesis

- Arises from pluripotential cells
- Arises from ductal and myoepithelial cells

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare; ~ 1-2% of all salivary gland tumors
- Age
 - Wide range, although usually in adults
 - Mean: 7th-8th decades
 - Rare, if at all, in children (probably represents sialoblastoma)
- Sex
 - Female > male (1.2:1)

Site

- Parotid gland most commonly affected (85-90%)
 - Usually superficial lobe
- Submandibular gland (~ 10%)
- Minor salivary glands (oral cavity usually), rare

Presentation

- Symptoms may be present for long duration (years)
- Painless swelling, enlargement or mass
 - Pain or tenderness is uncommon
- Brooke-Spiegler syndrome
 - Multiple skin adnexal tumors concurrent with BCAC

Treatment

- Surgical approaches
 - Complete local excision with free margins
 - May be more difficult to achieve in minor salivary gland locations
 - **No** enucleation or curettage
 - Neck dissection only in clinically positive cases
- Radiation
 - May be used for minor salivary gland tumors

- Carbon ion radiation for unresectable disease and postoperative gross residual or recurrent disease

Prognosis

- Considered low-grade malignant tumor, with good long-term prognosis
- May be locally destructive with recurrence
 - Up to 50% have recurrences, but up to 10 years after primary (indolent)
 - Highest in tumors of minor salivary glands
- Metastases uncommon
 - Most are to cervical lymph nodes (up to 15%), lung rarely
- Death from disease is rare (< 4%)
- Worse prognosis: Minor salivary gland, advanced stage, residual tumor at surgery, tumor recurrence

MACROSCOPIC

General Features

- Cut surface is homogeneous to focally cystic, gray-white to tan-brown
- Unencapsulated, circumscribed to infiltrative

Sections to Be Submitted

- Must include periphery to document invasion (parenchyma, soft tissue, nerve, vessels)

Size

- Variable, usually < 5 cm

MICROSCOPIC

Histologic Features

- Identical to basal cell adenoma, except for invasion
- Circumscribed, but tend to lack capsule
- Invasion **required** for diagnosis
 - Adjacent parenchyma, fat, skeletal muscle, dermis
 - Vascular invasion (~ 75% of cases)
 - Perineural invasion (~ 40% of cases)
- Necrosis can be seen (~ 45%)
 - Comedonecrosis, coagulative necrosis, apoptosis
- Multiple patterns of growth
 - Solid (most common)
 - Membranous (very thick collagenized matrix)
 - Tubulotrabeular
- Nests separated by eosinophilic basement membrane-like material
 - Collagenous septations
 - Thick, densely hyalinized basal lamina
 - Hyaline droplets or spheres within tumor nests
- Cluster or lobule formed by 2 cell populations
 - **Small, dark**, basaloid cells predominate
 - Uniform population with scant cytoplasm, indistinct cell borders, and round to oval basophilic nuclei
 - **Large, polygonal** cells
 - Ample eosinophilic to amphophilic cytoplasm
- Peripheral nuclear palisading at junction with stroma less conspicuous than in adenoma
- Lumen or duct formation (tubulotrabeular pattern)
 - Cuboidal, ductal cells surrounding lumen
- Nuclear pleomorphism is uncommon
- Mitotic figures: Range from 1-10/10 high-power field (HPF)

Immunohistochemistry Table

Antibody	Reactivity	Staining Pattern	Comment
CK-PAN	Positive	Cytoplasmic	All cells, but luminal (central) and ductal cells stronger
CK7	Positive	Cytoplasmic	Positive in many cases
CEA-M	Positive	Cytoplasmic	Highlights luminal cells preferentially
p63	Positive	Nuclear	Basal/myoepithelial cells
CK5/6	Positive	Cell membrane & cytoplasm	Highlighting areas of squamous differentiation
S100	Positive	Nuclear & cytoplasmic	Basal and myoepithelial cells; variable staining intensity
Calponin	Positive	Cytoplasmic	Basal/myoepithelial cells
Actin-HHF-35	Positive	Cytoplasmic	Basal/myoepithelial cells
Actin-sm	Positive	Cytoplasmic	Basal/myoepithelial cells
β-catenin	Negative		Lacks nuclear expression in most carcinomas
CD117	Positive	Cytoplasmic	Random cells positive in ~ 30% of cases
Bcl-2	Positive	Nuclear	> 50% of tumor cells in most cases

- Squamous differentiation is infrequently observed
- Lymphocytic and plasma cell infiltrate frequently present
- Hybrid tumors (BCAC with another tumor) very rare

ANCILLARY TESTS

Cytology

- Separation from basal cell adenoma is nearly impossible
- Smears are cellular, with irregular cohesive sheets, trabeculae and tubules, 3D clusters, and individual cells
- Homogeneous population of small, basaloid cells with high nuclear:cytoplasmic ratio
 - Nuclei are dense, round to ovoid
 - Naked nuclei are frequently present
- Globules or spheres of amorphous eosinophilic matrix material surrounded by tumor cells may be present

Immunohistochemistry

- Identifies dual differentiation: Ductal epithelial and basal myoepithelial
- Increased Ki-67 labeling index (> 5%) suggests carcinoma

Genetic Testing

- *PIK3CA* activating mutations detected, while *CTNNB1* mutations are not seen

DIFFERENTIAL DIAGNOSIS

Basal Cell Adenoma

- Circumscribed, without soft tissue infiltration, vascular &/or perineural invasion, and limited mitoses
- Multifocal or membranous type can simulate invasion
- **Nuclear** β-catenin can help with separation

Adenoid Cystic Carcinoma

- Very difficult to separate by core needle biopsy or FNA because both have uniform basaloid cells
- Cribriform pattern and pseudocysts filled with basophilic glycosaminoglycans
- Palisading is not prominent feature
- Lacks large pale and small dark cells common in BCAC

- High nuclear:cytoplasmic ratio; carrot-shaped, peg-shaped, or angular nuclei
- Coarse nuclear chromatin, high mitotic rate, necrosis

Pleomorphic Adenoma

- Multinodular and bosselated growth may simulate invasion
- Presence of myxochondroid matrix
- Plasmacytoid and spindled cells are frequent (rare in BCAC)
- Epithelial/myoepithelial cells blend into stroma, while BCAC has abrupt border with matrix

Basaloid Squamous Cell Carcinoma

- High-grade neoplasm, not primary salivary gland tumor
- Basaloid phenotype can be seen in both tumors
- Both have comedonecrosis and hyaline-type material
- Abrupt squamous differentiation: Keratinization, squamous cell carcinoma in situ, squamous cell carcinoma
 - Usually involves overlying surface mucosa

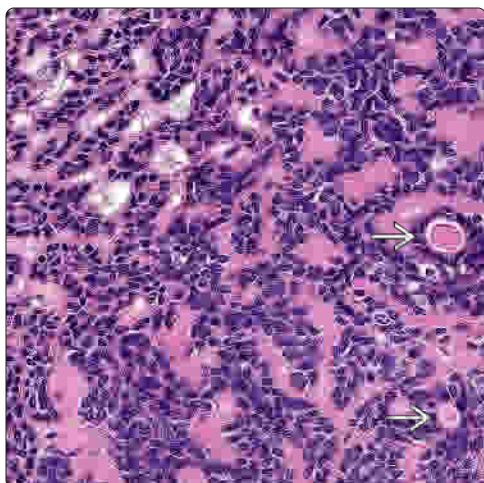
Metastatic Basal Cell Carcinoma

- Skin tumors may metastasize to intraparotid lymph nodes
- Lacks biphasic appearance and myoepithelial cells

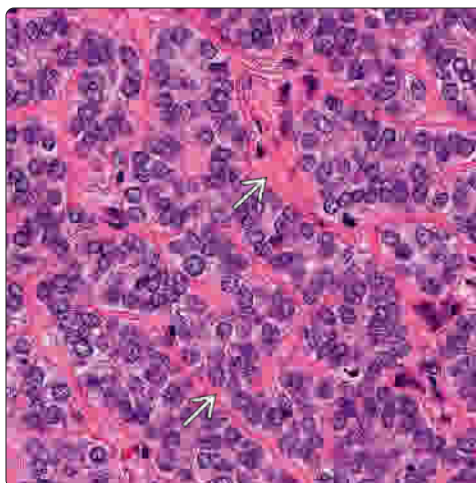
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Reduplicated Basement Membrane Material

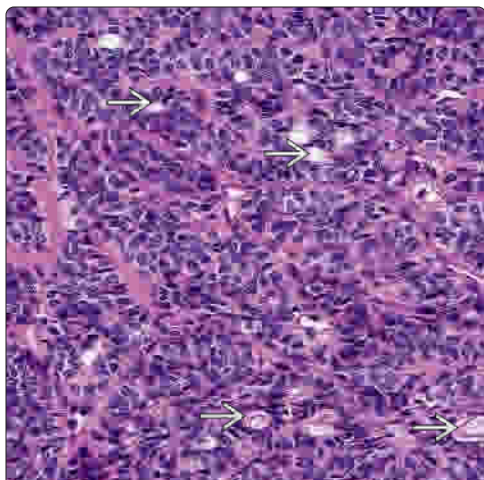


Trabecular and Tubular Architecture

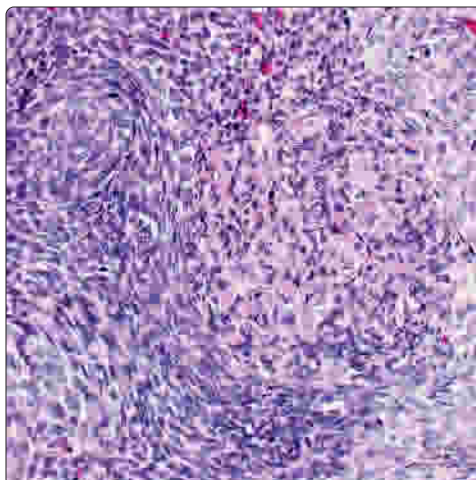


(Left) The thick, densely hyalinized basal lamina creates small tubules and rows of the neoplastic cells. Note an occasional lumen or duct formation within the neoplasm. Inspissated secretions are common. **(Right)** The neoplastic nests are separated by eosinophilic basement membrane-like material. The cells are small, uniform, dark basoloid cells, showing scant cytoplasm and indistinct cell borders.

Tubules With Ducts

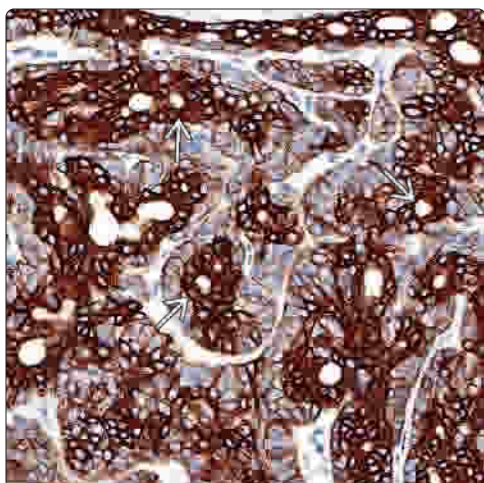


Basaloid Proliferation With Droplets

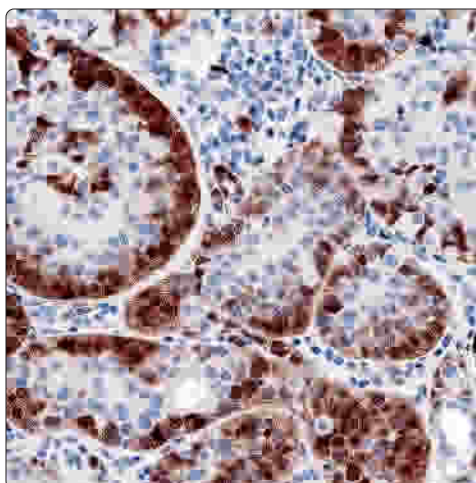


(Left) The eosinophilic basal lamina separates these tumor nests into islands. The cells show a suggestion of palisading. Tubules with lumina are noted throughout this neoplasm. **(Right)** The droplets, spheres, or globules of reduplicated basement membrane material area coalesced within this basaloid neoplasm. Note the spindled appearance to some of the basaloid cells.

Biphasic Staining With Pancytokeratin



Myoepithelial Cells Highlighted With S100 Protein



(Left) The keratin immunohistochemistry study highlights the luminal or tubular cells within the islands of the tumor. Keratin does not separate between the various cellular components of BCAC. **(Right)** S100 protein accentuated the myoepithelial cells in BCAC, and so will be noted at the periphery of the cell clusters. The central, luminal cells are not accentuated by this marker. Further, it could be used to highlight nerves around the tumor and document perineural invasion.

Oncocytic Carcinoma

KEY FACTS

TERMINOLOGY

- Malignant salivary gland epithelial tumor predominantly or exclusively composed of oncocytic cells with cytomorphic features of malignancy (adenocarcinomatous features) and invasive growth

CLINICAL ISSUES

- Occurs predominantly in parotid gland (80%)
- Mass or swelling ± associated pain &/or facial nerve paralysis
- May arise from longstanding benign oncocytoma or occur de novo
 - In association with oncocytoma, presents with rapid enlargement of preexisting mass lesion
- Total parotidectomy and nodal dissection given high incidence of regional (nodal) metastasis
- Guarded prognosis; tendency to recur, metastasize (locoregional, distant)






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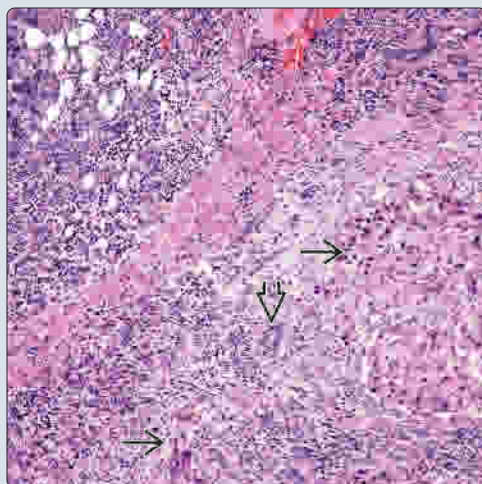
- Partially encapsulated or unencapsulated lesion showing varied growth patterns with invasive growth
 - Invasion includes into nonneoplastic salivary gland parenchyma, surrounding connective tissues, neurotropism, &/or angioinvasion
- Neoplastic cells are characterized by large, round to oval cells with abundant granular eosinophilic cytoplasm
- Nuclear pleomorphism varies from case to case and even within same case
 - Foci with absent nuclear pleomorphism may be seen near to or admixed with cells showing moderate to marked nuclear pleomorphism
 - Increased mitotic activity and necrosis may be present
- Clear cell change may be focal or more widespread

ANCILLARY TESTS

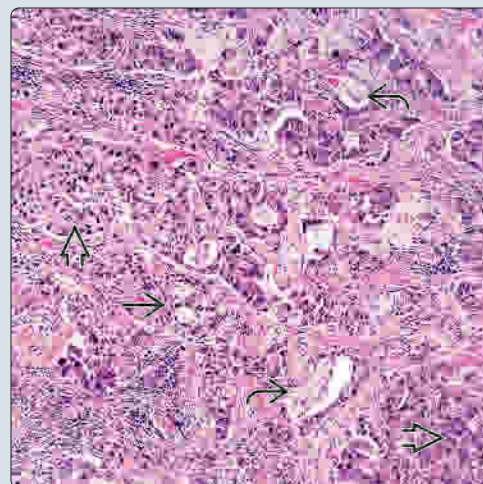
- Stains for epithelial mucin **negative**

Invasive Growth


(Left) At low magnification, this parotid unencapsulated tumor comprised of oncocytic cells with solid cell nests  is infiltrative into the nonneoplastic parotid parenchyma . Irrespective of cell type the presence of invasive growth is diagnostic for a malignant neoplasm. **(Right)** This oncocytic cell neoplasm is infiltrative with desmoplastic stroma and shows a variety of growth patterns, including glandular  and solid . Complex growth with back-to-back glands  is focally present.

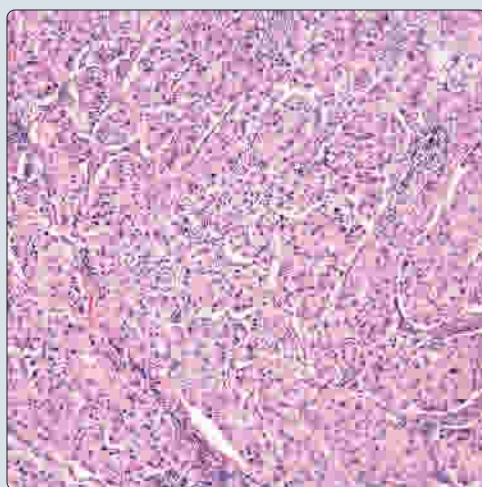


Invasive Growth

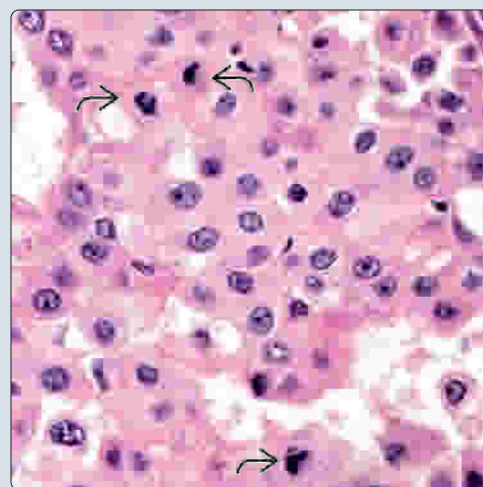


Growth Patterns

(Left) Additional growth patterns in oncocytic carcinoma may include trabecular and organoid. Irrespective of the pattern of growth, the neoplastic proliferation is entirely composed of oncocytic cells lacking diagnostic findings for an oncocytic variant of another tumor type (e.g., mucoepidermoid carcinoma). **(Right)** The cells in oncocytic carcinoma are characterized by prominent granular eosinophilic cytoplasm with round to oval nuclei, and enlarged eosinophilic nucleoli; mitotic figures are present .



Oncocytic Cells



TERMINOLOGY

Synonyms

- Malignant oncocytoma
- Oncocytic adenocarcinoma

Definitions

- Malignant salivary gland epithelial tumor predominantly or exclusively composed of oncocytic cells with cytomorphic features of malignancy (adenocarcinomatous features) and invasive growth

CLINICAL ISSUES

Epidemiology

- Incidence
 - Exceedingly rare tumor type representing < 1% of all salivary gland tumors
- Age
 - Most frequently occurs in 5th-8th decades of life
- Sex
 - Male > female

Site

- Occurs predominantly, but not exclusively, in parotid gland (80%)
 - Other sites of occurrence may include submandibular gland
 - Much less often in minor salivary glands

Presentation

- Mass or swelling ± associated pain &/or facial nerve paralysis
- May arise from longstanding benign oncocytoma or occur de novo
 - In association with oncocytoma, presents with rapid enlargement of preexisting mass lesion
 - Rare example arising from Warthin tumor
- Cervical lymphadenopathy at presentation fairly common

Treatment

- Surgical approaches
 - Total parotidectomy
 - Nodal dissection is advocated given high incidence of regional (nodal) metastasis
- Radiation
 - Efficacy of radiotherapy not definitively proven

Prognosis

- Guarded
 - Tendency to recur
 - Tendency to metastasize, including regional lymph nodes and distant metastases
 - Distant metastases occur to
 - Lungs
 - Kidney
 - Mediastinum
 - Liver
 - Bone
 - Thyroid gland
 - Distant metastasis is associated with poor prognosis, resulting in tumor-related death within 4 years

MACROSCOPIC

General Features

- Unencapsulated, single or multinodular, firm mass with tan-gray appearance
- Foci of necrosis may be present

MICROSCOPIC

Histologic Features

- Partially encapsulated or unencapsulated lesion showing varied growth patterns
 - Sheets and nests of neoplastic cells infiltrating surrounding tissues with loss of normal lobular architecture
- Neoplastic cells are characterized by large, round to oval cells with abundant granular eosinophilic cytoplasm
 - Nuclei enlarged, centrally located, round to oval with vesicular chromatin, often with prominent nucleoli
- Nuclear pleomorphism varies from case to case and even within same case
 - Foci with absent nuclear pleomorphism may be seen near to or admixed with cells showing moderate to marked nuclear pleomorphism
 - These features raise possibility of oncocytic carcinoma arising in association with oncocytoma
- Clear cell change may be focal or more widespread
- Increased mitotic activity and necrosis may be present
- Invasion includes infiltration of nonneoplastic salivary gland parenchyma, surrounding connective tissues, neurotropism, &/or angioinvasion

ANCILLARY TESTS

Cytology

- Aspirates show similar findings to those seen in oncocytoma
- Cytologic features indicative of malignancy include
 - Marked nuclear pleomorphism
 - Increased mitotic activity with atypical mitoses
 - Necrosis

Histochemistry

- Stains for mitochondria, including Novelli and phosphotungstic acid hematoxylin, show purplish and blue cytoplasmic granules, respectively
- Stains for epithelial mucin negative

Immunohistochemistry

- **Positive:** Cytokeratins including pancytokeratin (AE1/AE3), CK7, CK8, CK19
- CEA, EMA (+)
- **Negative:** S100 protein, p63, calponin, smooth muscle actin
- Increased proliferative activity as determined by Ki-67 (MIB-1) staining may be present

Electron Microscopy

- Numerous mitochondria that vary in size and shape
- Desmosomes, nearly continuous basal lamina, and lumina with microvilli are present

DIFFERENTIAL DIAGNOSIS

Oncocytoma

- Circumscribed to encapsulated lesion lacking
 - Significant nuclear pleomorphism
 - Increased mitotic activity
 - Invasive growth
- Oncocytic carcinoma with limited nuclear pleomorphism and mitotic activity occur but evidence of invasive growth is present
- Rare examples of (encapsulated) oncocytoma with metastatic tumor reported (so-called **metastasizing oncocytoma**)
 - Primary tumor showed minimal cytologic atypia; nodal metastasis at presentation; distant metastases months after diagnosis patient died 18 months after diagnosis

Oncocytosis

- Histologically, oncocytotic foci are
 - Unencapsulated
 - Appear in multiple (often 2 or more) separate nodules
 - Contain residual (nononcocytic) salivary gland parenchyma including
 - Ductular epithelium and serous acinar cells
 - Lack significant nuclear pleomorphism, mitotic activity, and invasive growth

Oncocytic Variants of Specific Malignant Salivary Gland Carcinomas

- Category of tumors that may include (among others)
 - Mucoepidermoid carcinoma
 - Acinic cell adenocarcinoma
 - Salivary duct carcinoma
- In order to render diagnosis of clear cell variant of specific malignant salivary gland tumor
 - Residual evidence of specific tumor type (e.g., mucoepidermoid carcinoma, others) must be identified
 - Acceptable even if residual focus of specific tumor type is only focally identified
- Salivary duct carcinoma
 - Often immunoreactive for androgen receptor, GATA3, &/or Her-2/neu
 - Such immunoreactivity not present in oncocytic carcinoma

Clear Cell Variants of Specific Malignant Salivary Gland Carcinomas

- Category of tumors that may include
 - Mucoepidermoid carcinoma
 - Acinic cell adenocarcinoma
 - Myoepithelial carcinoma
- In order to render diagnosis of clear cell variant of specific malignant salivary gland tumor
 - Residual evidence of specific tumor type (e.g., mucoepidermoid carcinoma, others) must be identified
 - Acceptable even if residual focus of specific tumor type is only focally identified

Metastatic Carcinoma

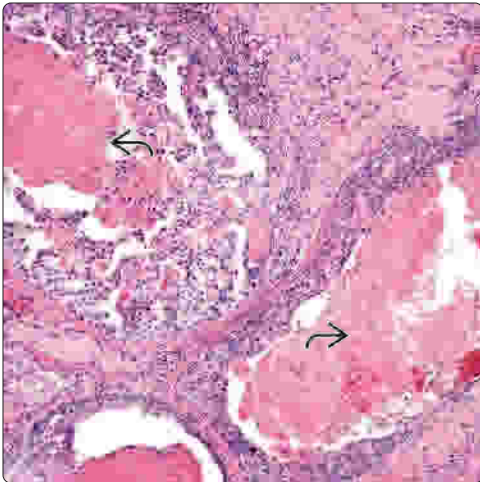
- Rare occurrence of metastatic carcinoma to salivary gland with oncocytic &/or clear cells

- Primarily includes renal cell carcinoma and less often thyroid carcinoma
- Metastatic renal cell carcinoma characterized by
 - Fibrovascular cores and centrally located red blood cells
 - Immunohistochemical reactivity for
 - CD10
 - Pax-2; pax-8
 - Renal cell carcinoma marker
 - CAIX
- Metastatic thyroid carcinoma shows
 - Immunohistochemical reactivity for
 - Thyroglobulin
 - TTF-1
 - Pax-8

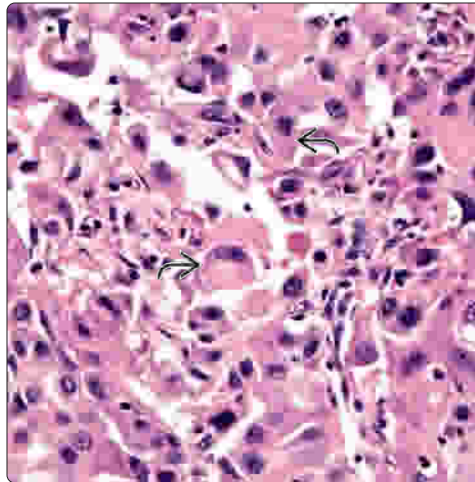
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Comedonecrosis

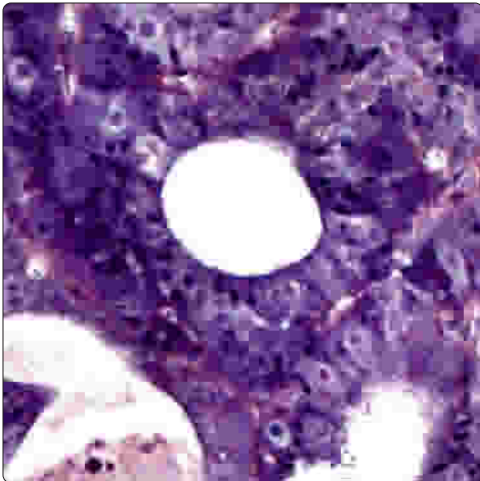


Oncocytic Cells

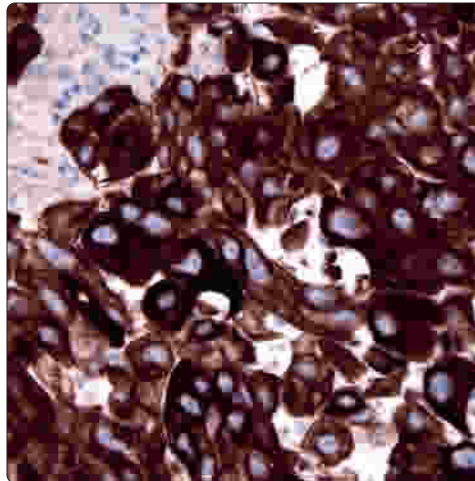


(Left) Cystic growth and central (comedo-type) necrosis [L] in oncocytic carcinoma may suggest a diagnosis of salivary duct carcinoma (SDC). (Right) Oncocytic carcinoma is comprised of cells with prominent, granular, eosinophilic-appearing cytoplasm [L]. Nuclear pleomorphism and hyperchromasia are present. These overall findings may suggest a diagnosis of SDC; in contrast to SDC, oncocytic carcinomas lack immunostaining for an androgen receptor, GATA3, and Her-2/neu.

Phosphotungstic Acid-Hematoxylin Staining

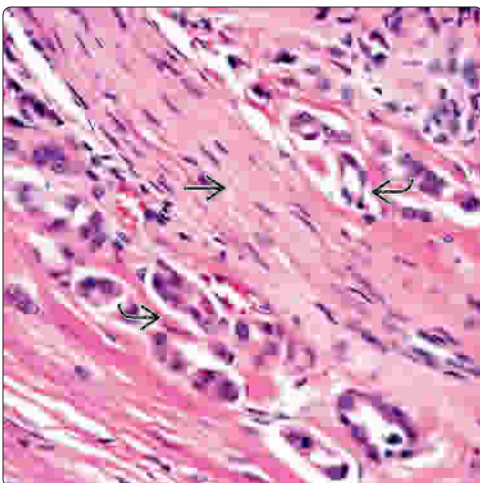


Cytokeratin Immunoreactivity

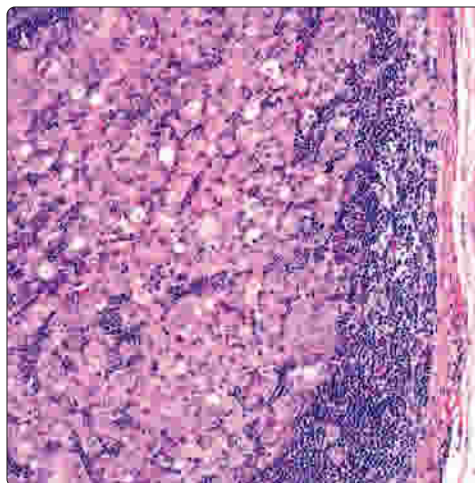


(Left) Phosphotungstic acid-hematoxylin stain demonstrates mitochondria as seen by intracytoplasmic (blue-black) granules in the oncocytic cells. (Right) The lesional cells in oncocytic carcinoma are diffusely and strongly reactive for cytokeratins, including AE1/AE3. There are no specific immunomarkers for oncocytic carcinomas, but the absence of p63 is helpful in differentiating oncocytic carcinoma from oncocytic variant of mucoepidermoid carcinoma.

Perineural Invasion



Nodal Metastasis



(Left) In any case, the cellular features of oncocytic carcinomas may be similar to oncocytomas. The presence of invasive growth, including lesional cells [L] adherent to nerves [L] (perineural invasion) would be diagnostic for oncocytic carcinoma. (Right) Metastatic oncocytic carcinoma to cervical neck lymph node is shown. Oncocytic carcinomas tend to metastasize early in the disease course to regional lymph nodes. Nodal dissection is advocated given the high incidence of regional (nodal) metastasis.

Sebacous Carcinoma and Sebaceous Lymphadenocarcinoma

KEY FACTS

TERMINOLOGY

- Sebaceous carcinoma (SC): Malignant epithelial neoplasm with focal areas of sebaceous differentiation
- Sebaceous lymphadenocarcinoma: Carcinoma arising from sebaceous lymphadenoma

CLINICAL ISSUES

- Bimodal peak: 3rd and 7th decades
- Overwhelming majority in parotid gland (> 90%)
- Painless, slow-growing, asymptomatic swelling or painful mass
- No relationship to Muir-Torre
- ~ 60-70% 5-year survival
- Recurrences: ~ 30%; metastases are uncommon

MICROSCOPIC

- Partially encapsulated, often well circumscribed
- Perineural invasion may be seen (~ 20%)
- Comedonecrosis may be seen

- Tumors form sheets, irregular islands, trabeculae, and large nests
- Ductal structures are common and may become cystic
- Sebocytes: Isolated, small clusters, large islands
 - Multivesicular and vacuolated clear cytoplasm
- Basaloid or squamous areas predominate
 - Basaloid areas predominate at nest periphery

ANCILLARY TESTS

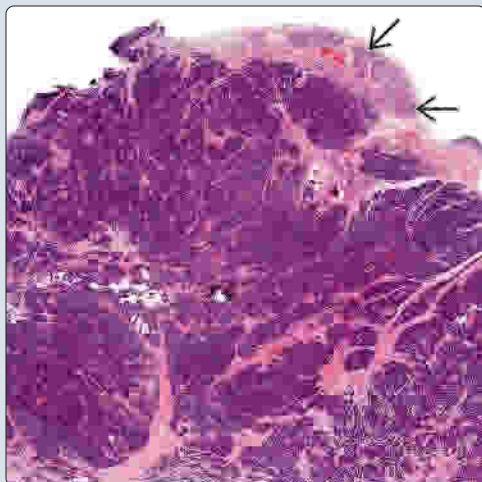
- Sebocytes: EMA (cytoplasmic vesicles highlighted), CD15, GCDFP-15
- Androgen receptor usually strongly **positive**

TOP DIFFERENTIAL DIAGNOSES

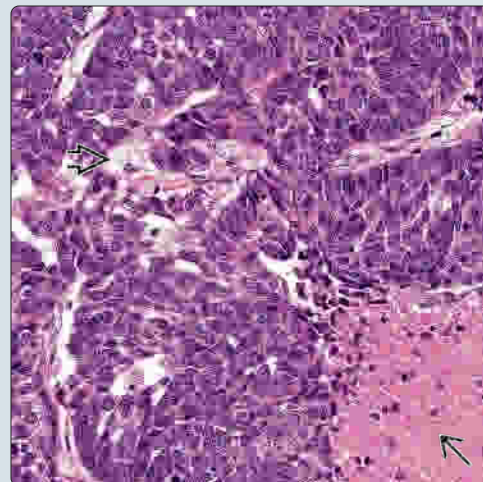
- Sebaceous adenoma
- Sebaceous lymphadenoma
- Direct extension from skin primary
- Sebaceous epithelial-myoepithelial carcinoma

Invasive Carcinoma With Fibrosis

(Left) A small portion of salivary gland parenchyma is present [1]. The tumor is unencapsulated and noncircumscribed. There is a lobular to sheet-like pattern, with bands of fibrosis dissecting between the tumor nests. (Right) A solid to trabecular sheet of basaloid neoplastic cells with an area of comedonecrosis [2] comprise this sebaceous carcinoma. Sebocytes [3] are infrequent in this area.

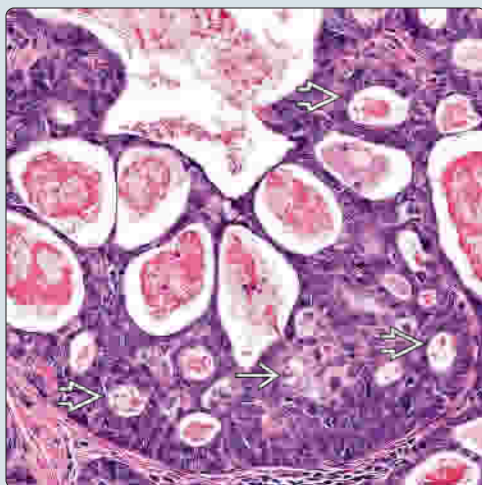


Comedonecrosis and Basaloid Cells

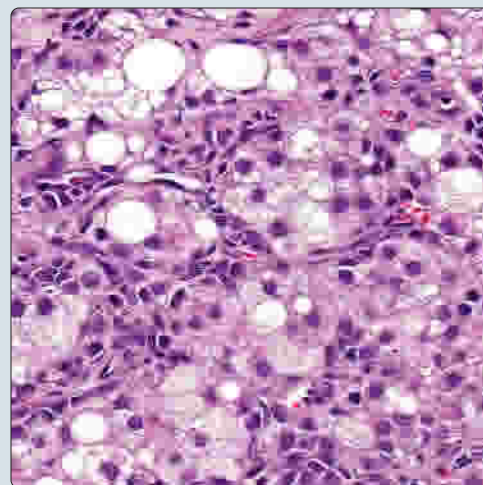


Cystic Areas With Rare Sebocytes

(Left) Areas of cyst formation are common in sebaceous carcinoma. Secretions are noted within the lumina. A rare sebocyte [4] is noted in this area of basaloid and ductal [5] differentiation. (Right) In this area of tumor, a basaloid periphery is noted surrounding large cells with multivesicular or multivacuolated cytoplasm. There is limited pleomorphism in this field.



Multivesicular Sebocytes With Mild Atypia



TERMINOLOGY

Definitions

- Sebaceous carcinoma (SC): Malignant epithelial neoplasm with focal areas of sebaceous differentiation
- Sebaceous lymphadenocarcinoma: Carcinoma arising from sebaceous lymphadenoma

ETIOLOGY/PATHOGENESIS

Cell of Origin

- Pluripotential cell
 - Sebaceous and glandular differentiation in same cell suggests pluripotential cell origin
 - Sebaceous cells seen in many salivary gland tumors

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very rare
- Age
 - Bimodal peak: 3rd and 7th decades

Site

- Overwhelming majority in parotid gland (> 90%)

Presentation

- Presentation is variable
 - Painless, slow-growing, asymptomatic swelling
 - Painful mass with possible facial nerve paralysis
 - Occasional fixation to skin
- No relationship to Muir-Torre

Treatment

- Radical surgical excision is treatment of choice
- Postoperative radiotherapy recommended for high-stage and high-grade tumors

Prognosis

- Considered intermediate-grade malignancy with guarded prognosis
- ~ 60-70% 5-year survival
- Recurrences: ~ 30%; metastases are uncommon
- Poor prognosis: Pleomorphism, facial nerve involvement

MACROSCOPIC

General Features

- Partially encapsulated, often well circumscribed, with pushing borders
- Variably yellow, tan, or gray-white

Size

- Range: 0.6-8.5 cm

MICROSCOPIC

Sebaceous Carcinoma

- Perineural invasion may be seen (~ 20%), but vascular invasion is uncommon
- Tumors form sheets, irregular islands, trabeculae, and nests
- Cords of tumor cells may extend into adjacent tissue
- Ductal structures are common and may become cystic

- Lining cells are cuboidal to low columnar without significant atypia
- Degree of sebaceous differentiation is very variable
 - Sebocytes: Isolated, small clusters, large islands
 - Multivesicular and vacuolated clear cytoplasm
- Basaloid or squamous areas predominate
 - Cellular pleomorphism variable, with large nucleoli
 - Most cells have large, hyperchromatic nuclei and clear to eosinophilic cytoplasm
 - Basaloid areas predominate at periphery of nests
 - Isolated mucocytes may be present
- Comedonecrosis (center of tumor islands) may be seen
- Lymphocytes may be present but not as germinal centers

Sebaceous Lymphadenocarcinoma

- Arise in association with sebaceous lymphadenoma or lymphadenoma
- Carcinoma is demarcated, lacking lymphoid stroma, showing invasion, pleomorphism, increased mitoses

ANCILLARY TESTS

Histochemistry

- Sebocytes positive with fat stains (oil red O, Sudan)

Immunohistochemistry

- Sebocytes: EMA (cytoplasmic vesicles), CD15, lactoferrin, GCDFP-15, androgen receptor

DIFFERENTIAL DIAGNOSIS

Sebaceous Adenoma

- Well-circumscribed with variably sized solid nests or cysts
- Peripheral epithelial cells are immature and surround variably developed sebaceous cells
- Lack cytologic atypia, invasion, and increased mitoses

Sebaceous Lymphadenoma

- Evenly distributed solid epithelial nests and cysts
- Cysts lined by bland squamoid, columnar, or cuboidal cells
- Sebaceous cells in solid nests or within cyst walls
- Background of uniformly dense lymphoid cells, often arranged in germinal centers

Direct Extension From Skin Primary

- Skin SC may directly invade salivary gland, requiring clinical and/or radiographic separation

Sebaceous Epithelial-Myoepithelial Carcinoma

- Sebaceous differentiation intermingled with areas of epithelial-myoepithelial carcinoma (focal or diffuse)
- Characteristic bilayered tubular structures with limited atypia
- SC lacks myoepithelial markers

SELECTED REFERENCES

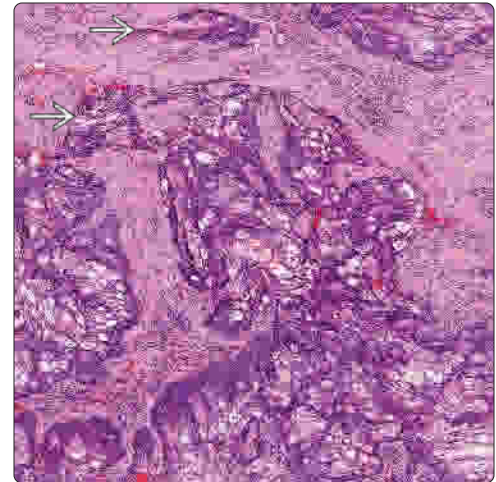
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CT of Right Parotid Gland Tumor

(Left) This CT demonstrates a tumor within the right parotid gland showing an area of cystic degeneration. However, this is nonspecific and does not help define the tumor type. (Right) Infiltration into the adjacent stroma is noted, along with a very heavy fibrosis. Even at this low magnification, cleared microvesicular cytoplasm can be seen as part of the sebaceous differentiation.

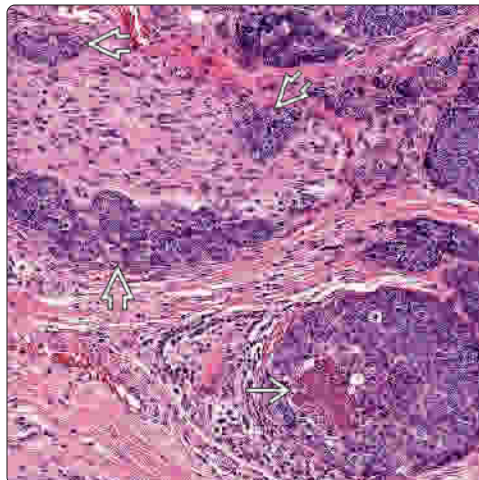


Heavy Stromal Fibrosis

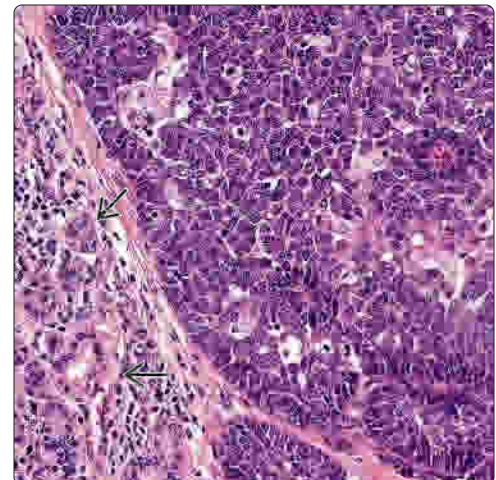


Perineural Invasion and Comedonecrosis

(Left) This case highlights a nerve showing multiple areas of perineural invasion, a feature seen in ~ 20% of tumors. There is also an area of comedonecrosis identified at the center of a tumor nest. These are helpful in confirming a malignant diagnosis. (Right) A remnant of salivary gland tissue is seen adjacent to the basaloid neoplastic proliferation. There is a vague palisading at the periphery of the tumor islands. While histiocytes are seen, no well-developed sebocytes are in this field.

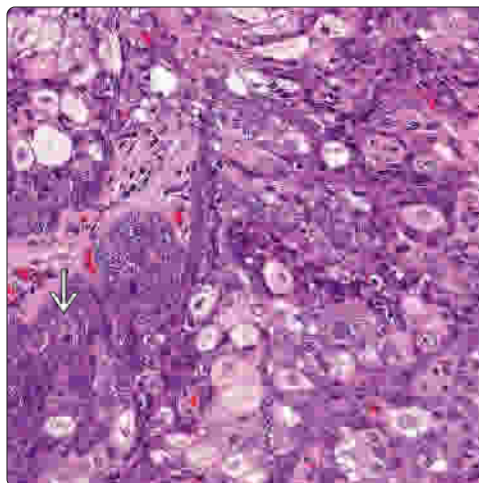


Basaloid Neoplastic Proliferation

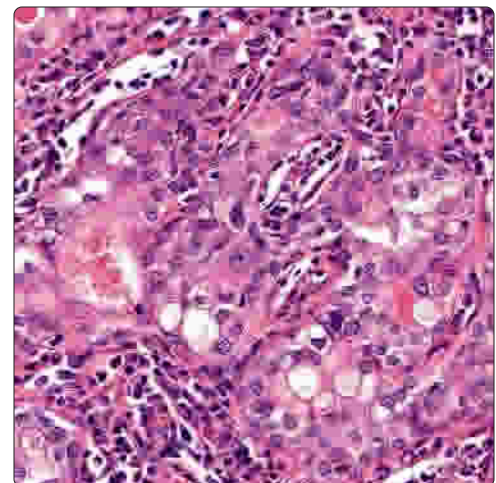


Pleomorphism and Mitoses in Sebaceous Carcinoma

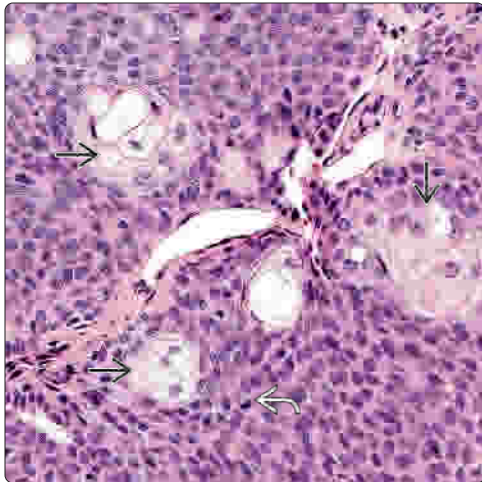
(Left) There is well-developed pleomorphism in this area of tumor, showing predominantly a basaloid phenotype. Sebocytes in clusters and individually are noted throughout. A mitosis is seen. (Right) This area shows a background of inflammatory elements intermingled with the neoplastic proliferation. This area shows a predominantly ductal and squamous appearance without well-developed sebaceous differentiation in this area.



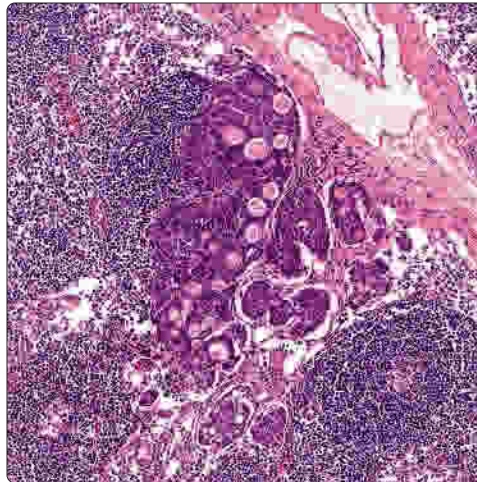
Ductal and Squamous Differentiation





Abrupt Sebaceous Differentiation

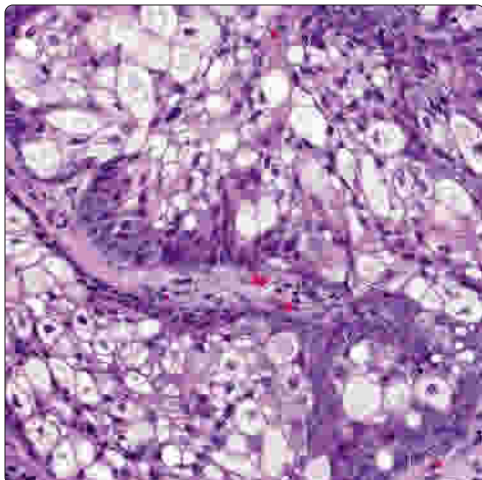


Metastatic Carcinoma in Lymph Node

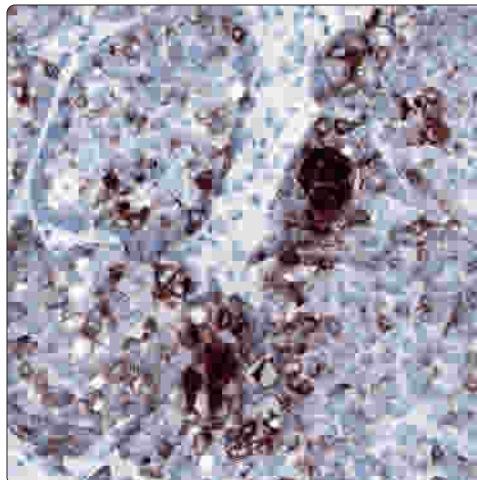


(Left) There are small collections of sebocytes  set in a tumor showing a predominantly squamoid appearance. The sheet of neoplastic cells has a pavement appearance, with isolated mitoses  (Right) The periparotid lymph nodes should be carefully examined, as metastatic foci from sebaceous carcinoma may be identified, as shown here. This tumor shows a basaloid and cystic pattern similar to what was seen in parts of the primary tumor.

Sebaceous Differentiation Is Prominent

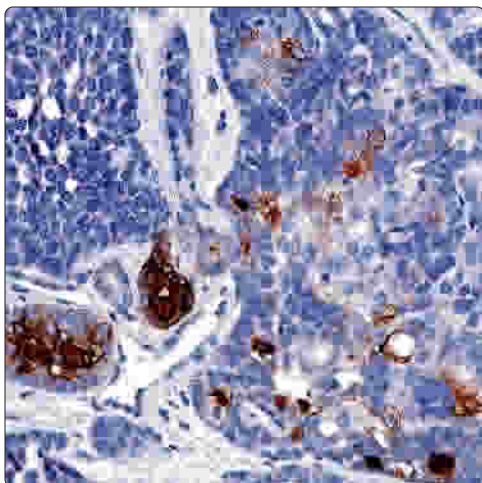


EMA Highlights Sebocytes Preferentially

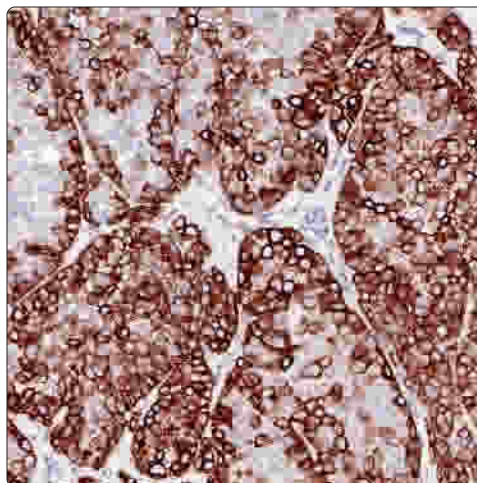


(Left) There is a rim of basaloid epithelium at the periphery of this tumor lobule. The dominant finding is the numerous sebaceous cells filling into the center of the lobule. (Right) EMA can be used to highlight areas of sebocytic differentiation, which show prominent deposition. In many cases, there is an accentuation of the cytoplasmic vesiculation.

GCDFP-15 Highlights Sebocytes



CK5/6 Highlights Many Cells



(Left) GCDFP-15 (BRST-2) is also used to highlight the sebocytes, as shown in this area. The background basaloid or squamoid cells do not stain with this marker. Therefore, it is important to review the entire tumor to find these areas of isolated immunoreactivity. (Right) The CK5/6 highlights the basaloid or squamoid areas, but does not tend to react with the sebocytes. There is often a peripheral palisaded predominance.

KEY FACTS

TERMINOLOGY

- Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (EMZBCL-MALT)
- Low-grade B-cell lymphoma arising at extranodal site (salivary gland), within marginal zone of reactive follicles

ETIOLOGY/PATHOGENESIS

- Sjögren syndrome nearly always precursor
 - Chronic antigen stimulation from autoimmune disease causes extranodal lymphoid tissue

CLINICAL ISSUES

- Female >> male
- Frequently, bilateral enlargement of parotid glands

MICROSCOPIC

- Diffuse or nodular pattern of growth
- Partial effacement of salivary gland parenchyma
- Lymphoepithelial lesions common (myoepithelial sialadenitis)

- Infiltration and distortion of epithelium by at least 3 neoplastic lymphoid cells
- Hyperplastic lymphoid follicles commonly seen, frequently colonized by neoplastic cells (nodular pattern)
- Expansion of marginal zone by heterogeneous cell population
 - Monocytoid cells (cleared), immunoblasts, centroblasts, plasmacytoid cells
- Transformation to DLBCL: Large cells arranged in sheets of > 20 cells

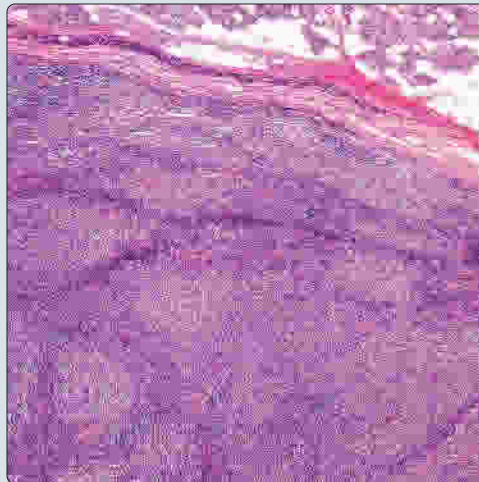
ANCILLARY TESTS

- **Positive:** CD20, CD19, CD79a, CD138, pax-5, CD22, Bcl-2
- Monotypic κ or λ light chains (usually plasmacytoid cells)
- Pancytokeratin highlights lymphoepithelial lesions

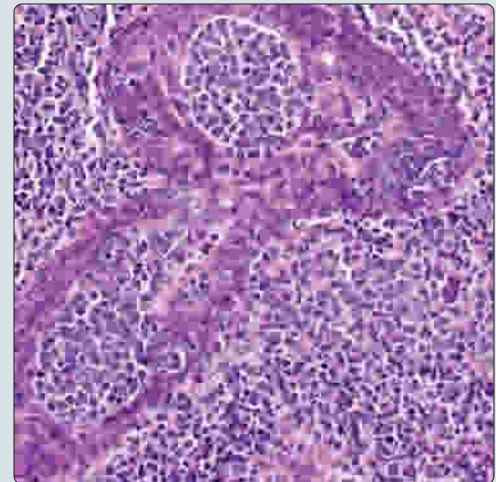
TOP DIFFERENTIAL DIAGNOSES

- Benign lymphoepithelial lesion, HIV-related lymph node changes, lymphoepithelial cyst, lymphadenoma, other lymphomas

Follicular Expansion Within Parotid Gland

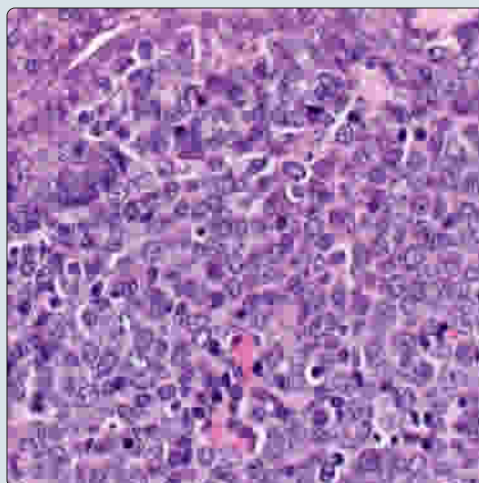


Lymphoepithelial Lesion

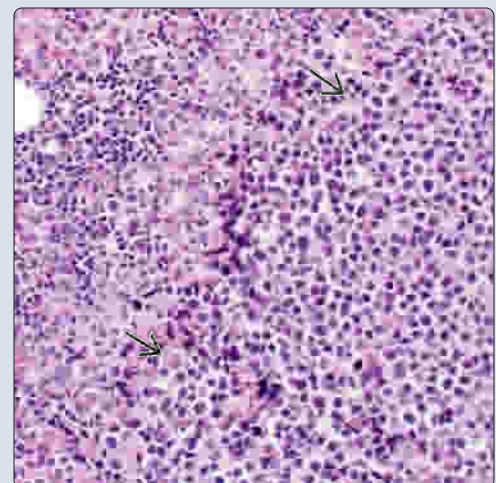


(Left) The salivary gland parenchyma is effaced by this nodular proliferation of lymphoid cells in this example of a follicle cell lymphoma affecting the parotid gland.
(Right) The ductal and acinar epithelium is invaded and partly destroyed by neoplastic lymphoid cells in this example of an extranodal marginal zone B-cell lymphoma of the parotid gland. This feature is very helpful in establishing the diagnosis.

Monocytoid Population



Diffuse Large B-Cell Lymphoma



(Left) The monocytoid B cells have a more cleared cytoplasm and are often seen immediately surrounding ducts, as noted in this case.
(Right) There is effacement of the salivary gland architecture by a diffuse sheet of greatly enlarged atypical lymphoid cells in this example of a diffuse large B-cell lymphoma.

KEY FACTS

TERMINOLOGY

- Tumors that secondarily involve salivary glands, which originate from, but are not in continuity with, primary malignancies of other sites

CLINICAL ISSUES

- 2-16% of all salivary gland tumors are metastatic/secondary tumors
- Older ages generally, correlated with increased malignancies of other anatomic sites
- Males > females for skin squamous cell carcinoma (SCC) and melanoma
- Parotid gland (intraparotid lymph nodes) >> submandibular or sublingual > oral cavity (minor salivary glands)
- ~ 60-70% are from cutaneous SCC
- ~ 20-30% are from melanoma (cutaneous, ocular)
- Remaining cases include breast, lung, kidney, colon
- Metastasis may be 1st manifestation of occult carcinoma

- Long-term prognosis is influenced by type and stage of tumor when 1st diagnosed

MICROSCOPIC

- Vascular-lymphatic metastases have different profile than direct extension
- Specific tumor type dictates histology
- Most common primary sites include
 - Cutaneous SCC, melanoma (conjunctival), renal cell carcinoma, small cell carcinoma (Merkel cell)

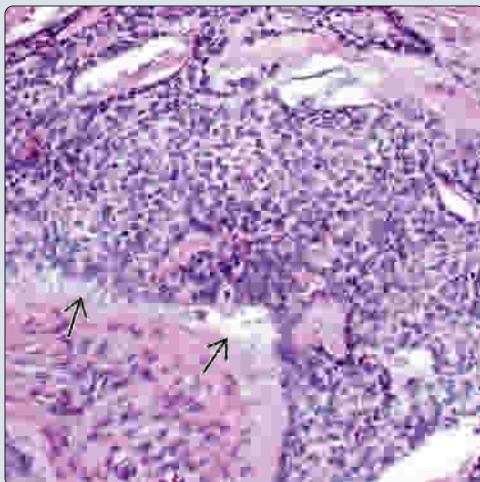
ANCILLARY TESTS

- Pertinent and targeted antibodies used to confirm metastatic disease

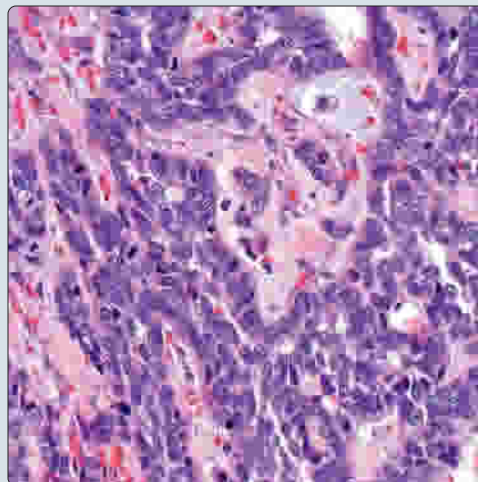
TOP DIFFERENTIAL DIAGNOSES


- Primary skin tumors, primary salivary gland tumors, direct extension

Skin Basal Cell Carcinoma

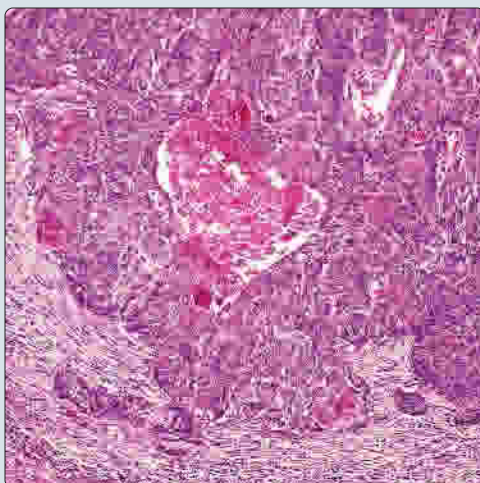


Metastatic Basaloid Squamous Cell Carcinoma

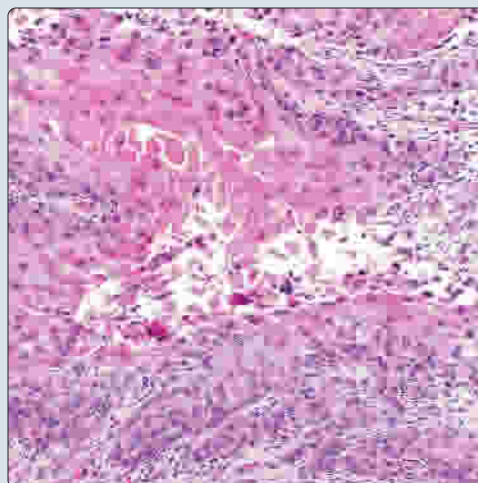


(Left) There is a characteristic epithelial to stromal clefting  that is commonly seen in cutaneous basal cell carcinoma. The proliferation is composed of basaloid cells with rather bland cytologic features. This could be metastatic or direct extension. (Right) This basaloid squamous cell carcinoma (SCC) was identified within the deep lobe of the parotid gland. The patient was known to have a tonsil basaloid SCC. As this tumor was within the gland, it was interpreted to be metastatic tumor.

Metastatic Squamous Cell Carcinoma



Keratinization in Metastatic Squamous Cell Carcinoma



(Left) The most common metastatic tumor the salivary gland is cutaneous SCC. Note the well-developed keratinization and keratin pearl formation, features usually not associated with mucoepidermoid carcinoma. (Right) There is abundant keratin formation in this SCC metastasis to the salivary gland. The patient had an ipsilateral scalp skin SCC.

PRIMARY TUMOR

Specimen

- Used for biopsies or resection of major salivary glands
 - Biopsy, parotidectomy (superficial or total), submandibular gland, sublingual gland, neck dissection
- Laterality: Right, left, or bilateral
- Exact tumor site should be stated
- Tumor focality (single, bilateral, multifocal)
- Tumor size: In centimeters
- Gross description: Encapsulated/circumscribed, invasive, solid, cystic

Histologic Type

- Many different primary tumor types
 - Acinic cell, adenoid cystic, mucoepidermoid, salivary duct, polymorphous low grade, myoepithelial, epithelial-myoepithelial, clear cell, oncocytic, mammary analogue secretory carcinomas, among others
- Adenocarcinoma not otherwise specified now has limited application and should only be used after extensive evaluation has been performed (immunohistochemistry, molecular) to document specific tumor type
- Carcinoma ex-pleomorphic adenoma must have extent of invasion, grade, and type of carcinoma component documented
- Metastatic tumors (melanoma, squamous cell carcinoma, Merkel cell carcinoma) to salivary gland are staged based on primary site (i.e., not salivary gland)

Histologic Grade

- Grades 1-3, with specific grading schemata for certain tumor types
 - Mucoepidermoid carcinoma
 - Adenoid cystic carcinoma
 - Adenocarcinoma, not otherwise specified
 - Carcinoma ex-pleomorphic adenoma

Invasion

- Lymphovascular invasion
- Perineural invasion

- Margin assessment
 - Distance to closest margin (oriented if possible) in millimeters

Additional Findings

- Sialadenitis, tumor-associated lymphoid proliferation, among others
- Identification of special studies, if performed
- Neoadjuvant therapy, if given, specifying type

REGIONAL LYMPH NODES

Cervical Lymph Nodes: Unilateral or Bilateral

- Separated into pN0, N1, N2 (a, b, c), and N3 based on number and size of lymph nodes affected
- N1: 1 ipsilateral lymph node < 3 cm
- N2: 1 ipsilateral lymph node > 3 ≤ 6 cm, or multiple ipsilateral, bilateral, contralateral lymph nodes ≤ 6 cm
- N3: Metastases in lymph node > 6 cm
- Extracapsular extension for all lymph nodes evaluated is reported

PROGNOSTIC GROUPS

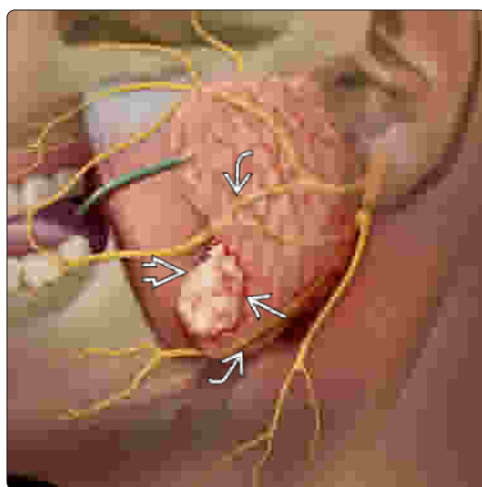
T1 to T4 Categories

- T1: Tumor ≤ 2 cm without extraparenchymal extension (macroscopic)
- T2: Tumor > 2 ≤ 4 cm without extraparenchymal extension (macroscopic)
- T3: Tumor > 4 cm &/or extraparenchymal extension
- T4: Advanced disease
 - T4a: Invades skin, mandible, ear canal, &/or facial nerve
 - T4b: Invades skull base &/or pterygoid plates &/or encases carotid artery

SELECTED REFERENCES

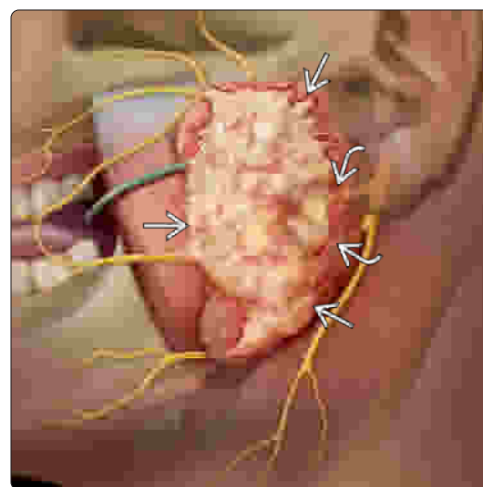
1. Seethala RR: Histologic grading and prognostic biomarkers in salivary gland carcinomas. *Adv Anat Pathol.* 18(1):29-45, 2011
2. Vander Poorten VL et al: Prognostic index for patients with parotid carcinoma: external validation using the nationwide 1985-1994 Dutch Head and Neck Oncology Cooperative Group database. *Cancer.* 97(6):1453-63, 2003

T3 Salivary Gland Primary Tumor

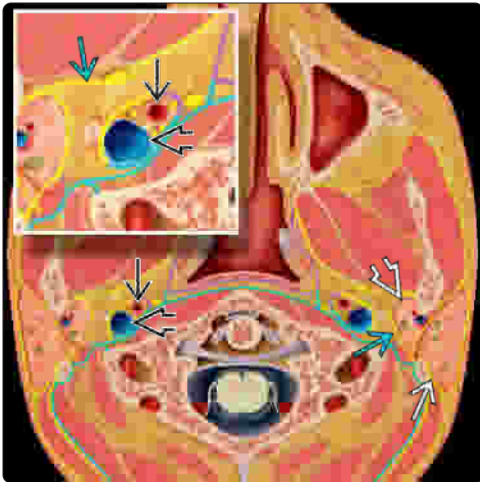


(Left) Graphic illustrates a small parotid tumor that is designated T3 because it extends from the gland to extraparenchymal tissue clinically. There is, however, no involvement of facial nerve branches. (Right) Graphic illustrates a large superficial parotid gland tumor. A lesion > 4 cm would be at least a T3 tumor, but involvement of the facial nerve branches increases the tumor to a T4a moderately advanced tumor. (Cranial nerve = CN.)

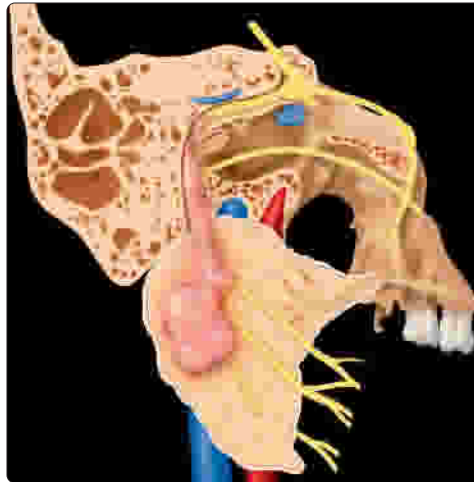
T4a Primary Tumor With CN VII Invasion



Axial Graphic of Salivary Gland Anatomy

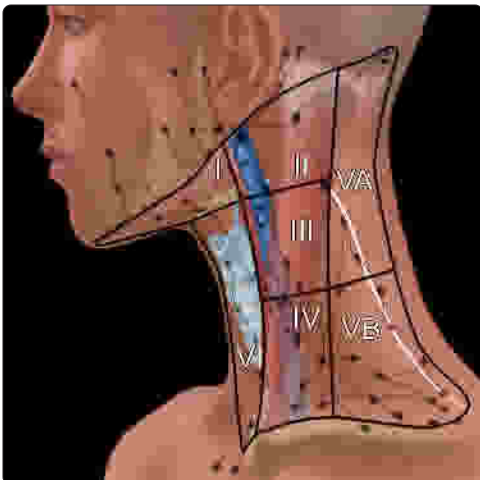


Perineural Involvement of Facial Nerve

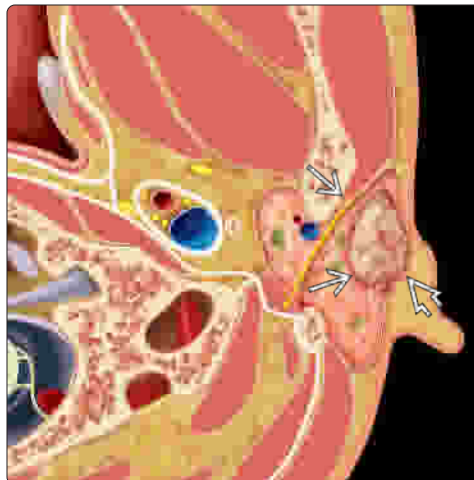


(Left) There is an intimate relationship between the superficial and deep lobes of the parotid gland, with surrounding bone, facial nerve branches, carotid artery, and jugular vein, as well as muscle bellies. All are taken into consideration with staging. (Right) The facial nerve and branches are intimately associated with the superficial and deep lobes of the parotid gland. A tumor in this location (especially adenoid cystic carcinoma) can track up the nerve, deep into the temporal bone.

Lymphatic Drainage to Cervical LNs

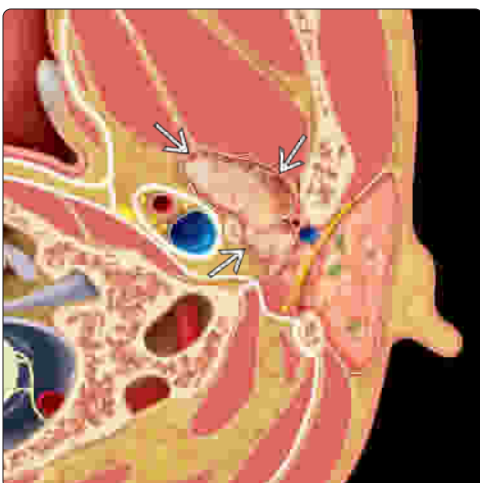


Graphic of pT3 Parotid Tumor

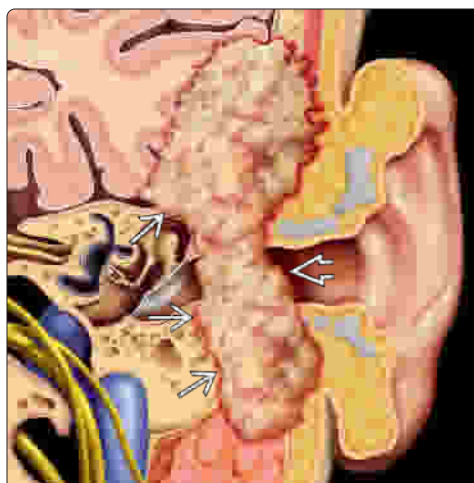


(Left) The cervical lymph nodes (LNs) are separated into zones (I to VI), which describe the most common drainage sites for certain malignancies. Compartment designations are useful in staging all salivary gland tumors. (Right) Axial graphic shows a tumor that extends beyond the gland into extraparenchymal tissue. T3 salivary tumors are > 4 cm in size or grossly extend beyond the gland no matter what the size.

pT2 Deep Parotid Lobe Tumor



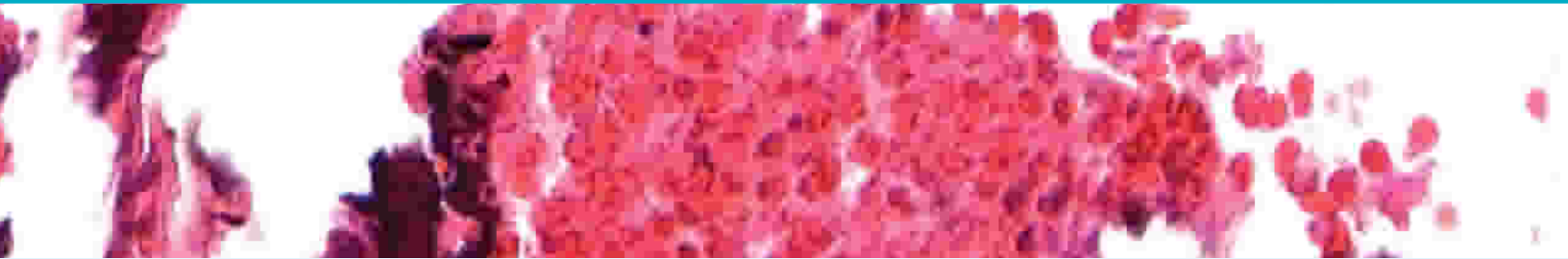
Coronal View of T4b Parotid Gland Tumor



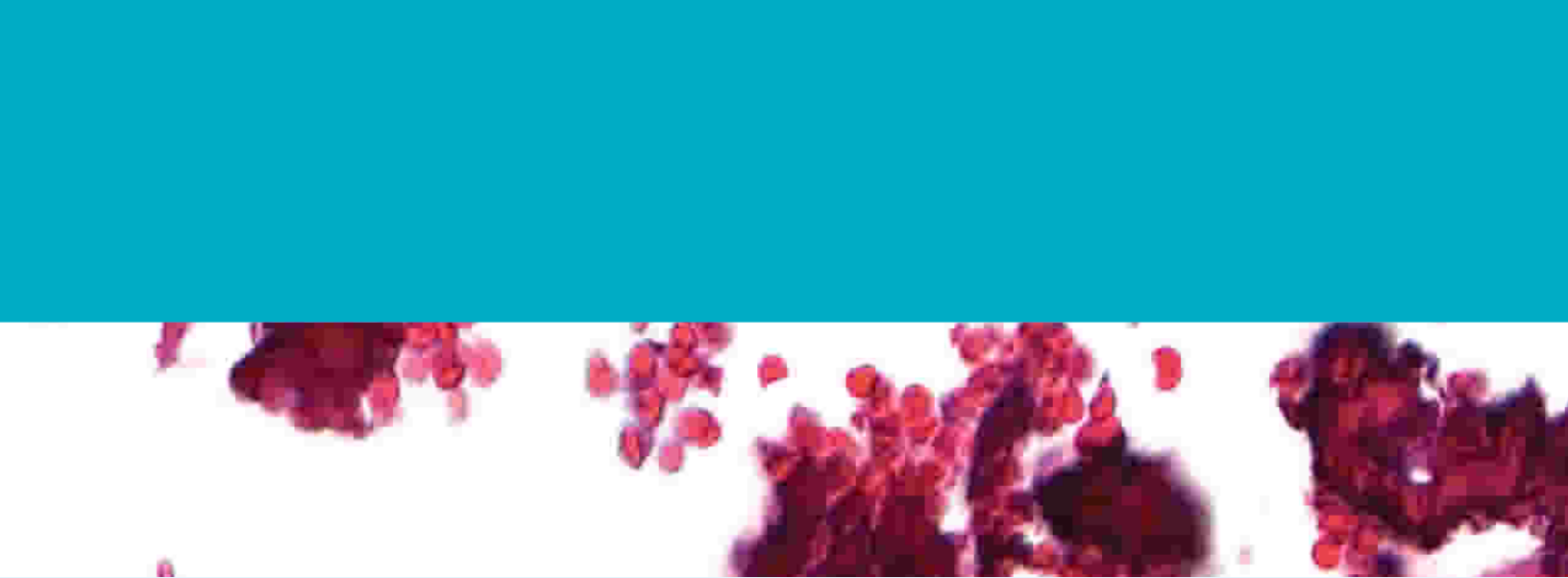
(Left) Axial graphic illustrates a tumor arising within the deep lobe of parotid gland. T2 tumors are > 2 ≤ 4 cm in greatest size, without gross extension beyond the gland. (Right) Coronal graphic illustrates another T4b tumor with extensive skull base and external auditory canal invasion. T4b is determined by invasion of skull base, pterygoid plates, &/or encasement of the carotid artery.

SECTION 6

Jaw



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MACROSCOPIC ANATOMY

Crown

- Part of tooth easily seen clinically
- Surfaced by hard, brittle, translucent enamel supported by underlying dentin
- Pulp forms central chamber of tooth that supplies nutrition and contains nerve supply

Root

- Anchors tooth to alveolar bone, number varies depending on tooth
- Apical foramen is opening through which blood and nerve supply enter and exit tooth

MICROSCOPIC ANATOMY

Enamel

- Acellular, highly mineralized, 96% inorganic material made up of hydroxyapatite crystals
- Crystals are aligned to create rods
- Immature enamel has basophilic, fish scale appearance

Dentin

- 70% mineralized tissue
- Eosinophilic, closely packed tubules
- Odontoblasts are responsible for production of dentin, and their processes occupy tubules
- Reparative dentin deposited at site of injury shows distorted tubular pattern

Pulp

- Loose connective tissue that resembles primitive mesenchyme
- Odontoblasts line pulp chamber
- Stellate fibroblasts, small blood vessels

Periodontal Ligament

- Thin fibrous attachment between root and bone
- Permits slight movement of teeth
- Seldom preserved or seen on routine processing

Cementum

- Mineralized organic material that resembles bone
- Cementocytes are responsible for production of cementum and occupy its lacunae
- Where enamel and cementum meet (or overlap) is referred to as cemento-enamel junction

PITFALLS/ARTIFACTS

Issues With Processing of Hard Tissues

- Teeth need to be decalcified for routine H&E slides
 - Mature enamel is lost to processing

AGE VARIATION

Primary (Deciduous)

- 20 teeth: Smaller in size, erupt between 6-30 months of age
 - 8 incisors, 4 canines, 8 molars

Secondary (Permanent)

- 32 teeth: Larger in size, erupt starting at ~ 6 years of age
 - 8 incisors, 4 canines, 8 premolars, 12 molars






Changes Found in Both Primary and Secondary Teeth

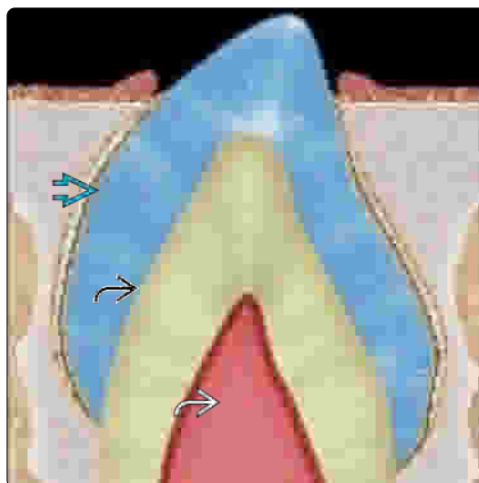
- Hyperdontia (supernumerary teeth)
- Hypodontia
- Dentin continues to be laid down with age, reducing size of dentin tubules and shrinking pulp chamber
- Attrition: Loss of tooth due to tooth-to-tooth contact
- Abrasion: Loss of tooth due to tooth-to-non-tooth contact
- Erosion: Loss of tooth structure due to chemical process
- Caries: Loss of tooth structure due to bacterial decay
- Teeth generally darken with age
- Dental restorations may alter or replace normal histology
- Teeth may be lost due to disease or trauma

SELECTED REFERENCES

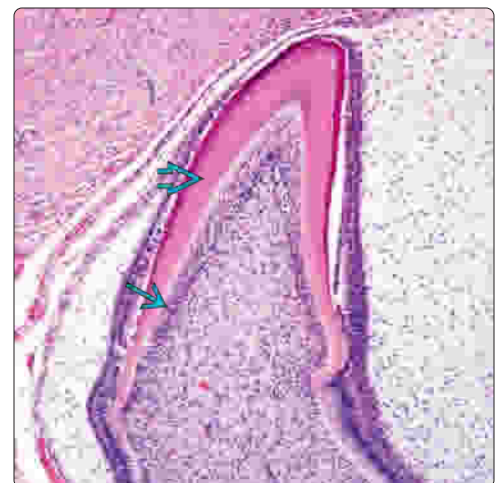
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2. Ten Cate AR: Oral Histology: Development, Structure, and Function. 3rd ed. St. Louis: Mosby, 1989

Graphic of Tooth Major Components

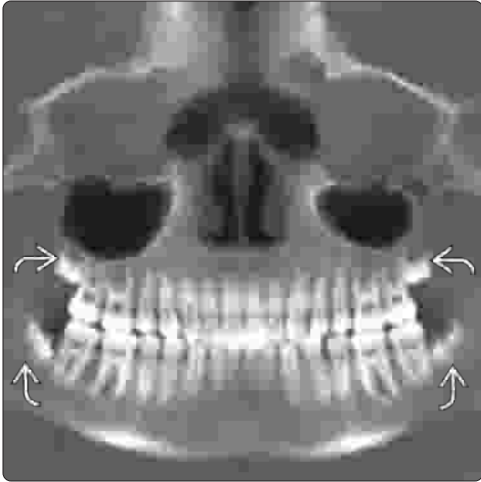
(Left) This graphic shows the major components of a tooth. Enamel  surfaces the crown and is supported by underlying dentin . The pulp  is found centrally and contains the blood and nerve supply for the tooth. Infection or injury to the pulp may result in swelling and possibly the devitalization of the tooth. (Right) This image shows the developing tooth and some of its components. Dentin  is being produced by odontoblasts  found on the periphery of the pulp tissue.



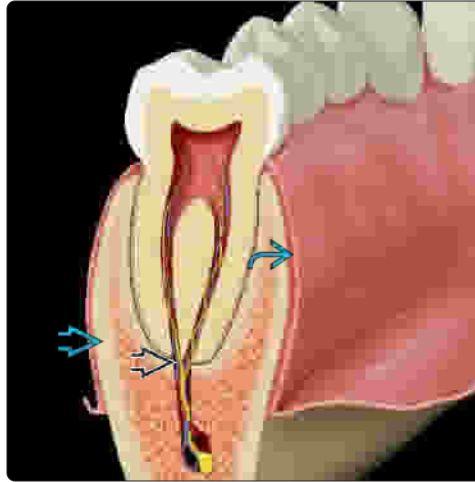
H&E of Tooth Major Components



Normal Full Dentition: Young Adult



Cross Section of the Jaw and Teeth

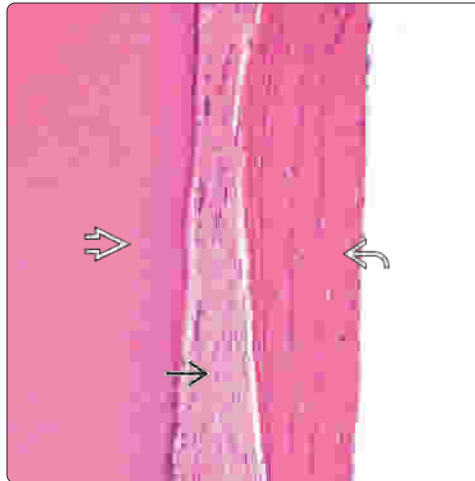


(Left) This image shows the normal full dentition of a young adult. Note that the 3rd molars are yet unerupted. The eruption of the 1st permanent teeth begins around age 6, with the 1st molars, and generally ends in the early 20s with the eruption of the 3rd molars. (Right) This graphic shows a molar supported by surrounding bone and healthy gingiva. Note the blood and nerve supply entering and exiting the tooth at the apex.

Dentin-Pulp Complex

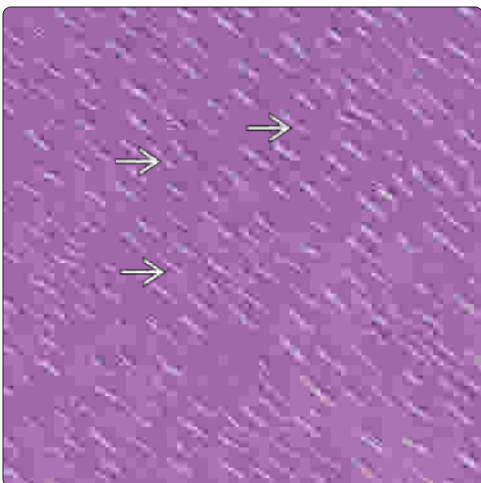


Periodontal Ligament



(Left) This high-power image shows the dentin-pulp complex. The odontoblasts form a single layer along the periphery of the pulp and have processes that extend into the tubules. It is the presence of these cells and their processes that makes dentin a sensitive tissue. (Right) The periodontal ligament (PDL) provides attachment between the tooth root and the surrounding alveolar bone. The PDL is made up of fibrous connective tissue that allows for slight movement during normal eating and biting.

Dentin Histology



Enamel Matrix Histology



(Left) A high-power longitudinal section of dentin shows the slight curvature of the tubules. These tubules are filled with fluid and odontoblast processes. The tubules, however, make the dentin vulnerable to invasion of bacteria, which may result in dental caries and infection of the pulp. (Right) A high-power view shows a classic, basophilic, fish-scale appearance of the enamel matrix. Mature enamel, unlike matrix, is destroyed by routine tissue processing.

KEY FACTS

TERMINOLOGY

- Inherited disease characterized by progressive, painless, symmetrical expansion of the jaws, resulting in a cherubic facial appearance

CLINICAL ISSUES

- Autosomal-dominant hereditary childhood disease with variable expression
- Nearly always identified before 5 years of age
- Male > female (2:1)
- Mandible affected most commonly
- Great variation in clinical expression
- Symmetrical, hard, and painless swelling of the jaws described as angel-like
- No specific uniform treatment
 - Generally, watchful waiting for spontaneous regression/involution in adulthood
 - Radiation absolutely **contraindicated**

IMAGING

- Bilateral, multilocular, radiolucent areas within gnathic bones



MICROSCOPIC

- Histologic appearance is **not** diagnostic without clinical and radiographic findings
- Highly vascular fibrous stroma (fibroblasts) arranged in whorled pattern
- Numerous osteoclastic-type multinucleated giant cells with prominent nucleoli
 - Giant cells arranged near hemorrhagic foci
- Perivascular eosinophilic collagen cuffing around small capillaries primarily

TOP DIFFERENTIAL DIAGNOSES

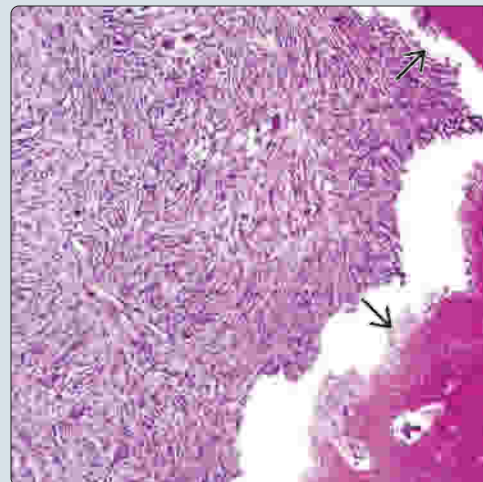
- Fibrous dysplasia, infantile cortical hyperostosis, hyperparathyroidism, giant cell tumor, Noonan syndrome

Axial CT of Cherubism




(Left) Axial bone CT from a patient with cherubism shows the posterior mandible that is affected bilaterally with expansion and appears multiloculated . Usually the expansion is symmetrical and tends to involve the angles and ascending ramus. In some cases the entire mandible can be affected. The maxilla can also be affected. (Right) Cherubism often appears as a spindle cell lesion with resorption of the adjacent bone  and subsequent re-formation of the bone, leading to "expansion" of the bone clinically and radiographically.

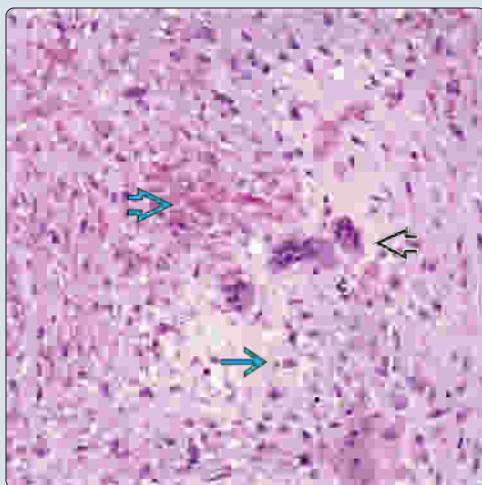


Bone Resorption and Reformation

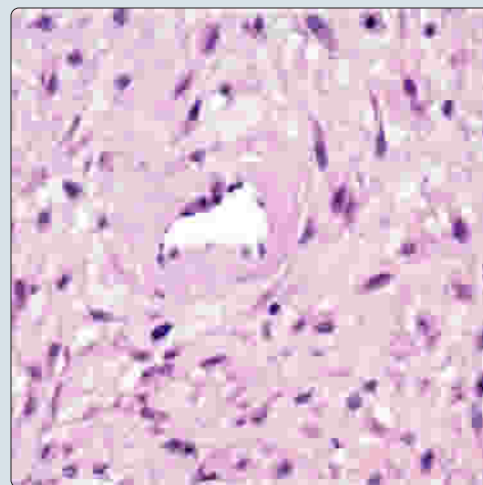


Giant Cells in Cherubism

(Left) The stroma in cherubism is often more loosely arranged than central giant cell granulomas. Extravasated erythrocytes  and hemosiderin pigment  is often seen along with scattered multinucleated giant cells . In older lesions of cherubism the stroma is more fibrotic and new bone formation is seen. (Right) Although not present in all cases of cherubism, eosinophilic cuff-like deposits around blood vessels is specific for the disease and not present in central giant cell granulomas.



Perivascular Eosinophilic Cuffing



KEY FACTS

TERMINOLOGY

- Torus palatinus (TP) refers to bony growth arising in midline of hard palate
- Torus mandibularis (TM) refers to bony growth arising in lingual mandible above mylohyoid bone

CLINICAL ISSUES

- Usually 1st noted in early adult life
- TP and TM: Lesions can usually be diagnosed clinically and are asymptomatic
- No reports of malignant transformation
- Similar to jaw bones, bisphosphonate related osteonecrosis can involve tori
- Surgical removal necessary only when bony protuberance interferes with dental function
 - May experience regrowth after removal

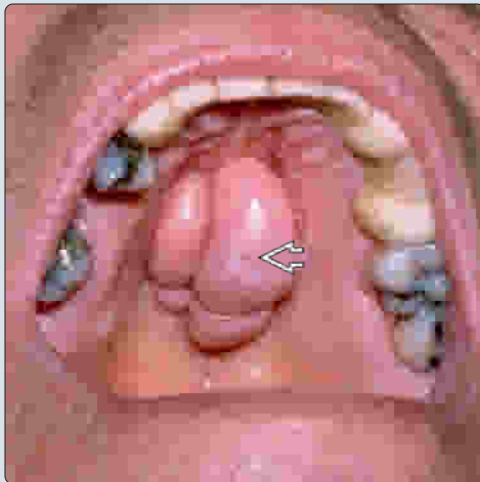
MICROSCOPIC

- Dense, mature lamellar bone with minimal osteoblastic activity
- May have small fibrofatty marrow spaces
- Some cases may have dense cortical bone overlying trabecular (cancellous) bone

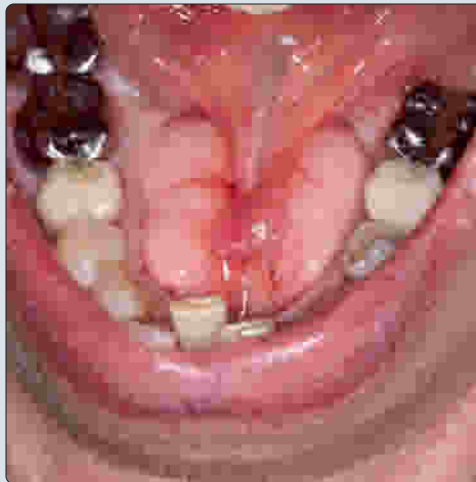
TOP DIFFERENTIAL DIAGNOSES

- **Buccal exostosis**
 - Common bony growths along facial aspect of maxilla &/or mandible
 - Histology identical to TP and TM
- **Osteoma**
 - Seen in craniofacial skeleton, including jaws
 - Usually solitary and asymptomatic
 - Multiple osteomas are associated with Gardner syndrome
 - Histology identical to TP and TM, although perhaps with more osteoblastic activity

Lobulated Torus Palatinus



Torus Mandibularis

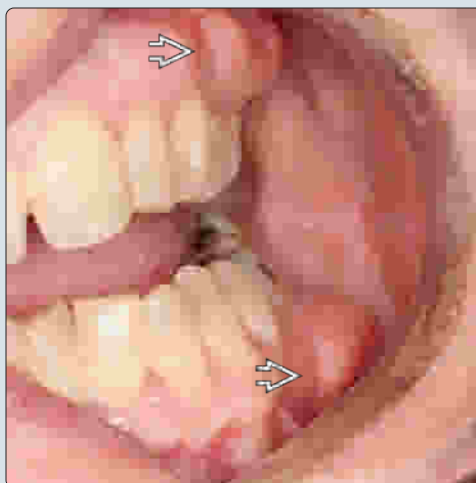


(Left) Torus palatinus presents as a large, lobulated palatal mass that is bony hard. Because of the large size of this torus, it is subject to trauma; the thin overlying mucosa can ulcerate [1]. (Right) Clinical photograph shows bilateral bony protuberances along the lingual mandibular alveolar ridge. Bilateral involvement occurs in more than 90% of cases. The tori may present as a single lobule or as multiple lobules. The tori can become quite large with instances of the tori almost touching in the midline.

Dense Cortical Bone



Buccal Exostoses



(Left) High-power photomicrograph of a decalcified torus is composed of dense cortical lamellar bone [2]. Fatty marrow is evident and associated with trabecular bone, a feature not always present [3]. (Right) Clinical photograph shows multiple maxillary and mandibular buccal exostoses [4]. The bony protuberances are lobulated. These lesions are generally asymptomatic, although, due to the thin mucosal covering, are susceptible to trauma from toothbrushing and eating, and can become ulcerated.

KEY FACTS

TERMINOLOGY

- Osteomyelitis is infection of bone and bone marrow with multiple classification schemes

CLINICAL ISSUES

- In general, uncommon disease in head and neck
- In general, all ages can be affected
- Fever, chills, irritability or lethargy, malaise, pain, headache, cranial neuropathy
 - Subacute/chronic symptoms are not characteristic
- Mandible: Most commonly affected maxillofacial area; odontogenic infections and fractures are predisposing factors
- Maxilla: More commonly affected in children
- Bone scan is most sensitive study for early disease
- Important to culture causative organism by percutaneous or open biopsy
- Surgery to remove dead bone with targeted intravenous antimicrobial therapy

MICROSCOPIC

- Marrow fibrosis or edema is hallmark
- Bone marrow fibrosis, bone death, and resorption
- Acute: Neutrophilic infiltrate with delicate marrow fibrosis or edema
- Subacute: Infiltrate of both neutrophils and chronic inflammatory cells
- Chronic: Chronic inflammatory infiltrate and fibrosis

ANCILLARY TESTS

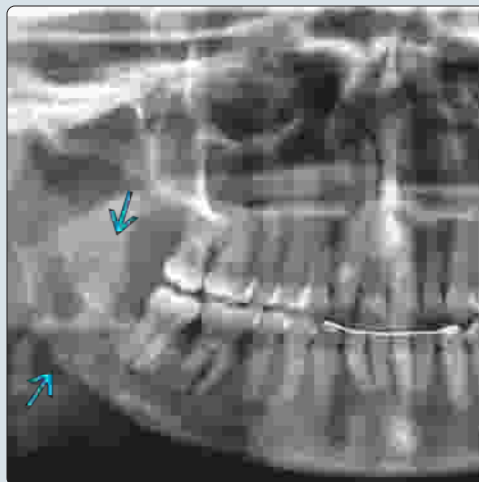
- Gram, acid-fast, fluorostain, GMS, and PAS-LG (among others) highlight organisms

TOP DIFFERENTIAL DIAGNOSES

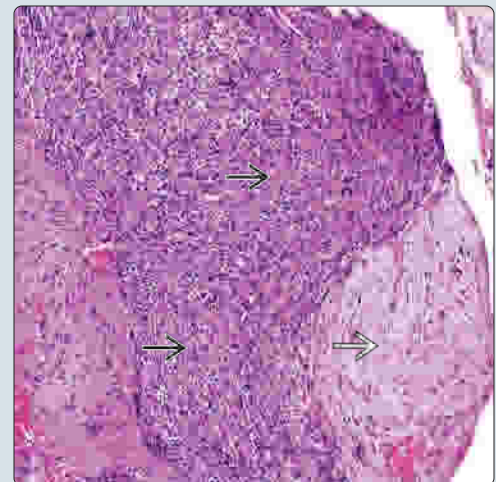
- Inflammatory reaction, lymphoma, sarcoid, bisphosphonate therapy, radiation osteitis

Osteomyelitis of Right Mandible

(Left) This 20-year-old woman with osteomyelitis reported pain for over a year and failed surgical and drug therapy. She went on to have a partial resection of her mandible followed by reconstruction. Her treatment was complicated by a dependence on pain medications she developed while being managed for her osteomyelitis. (Right) Inflammation, especially acute, is often associated with fibrin deposition and associated delicate fibrosis. Bone is not visible, as it may be completely resorbed.

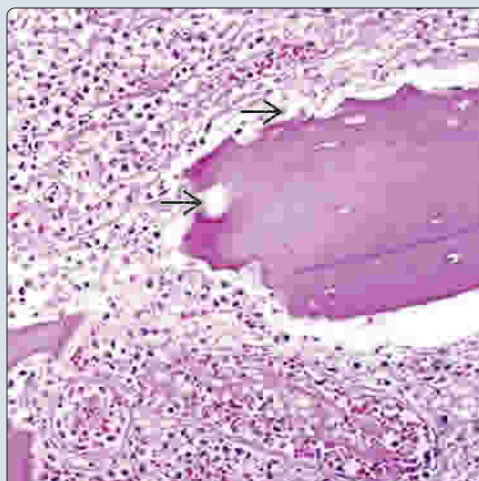


Fibrin Deposition in Acute Infection



Necrosis of Bone Marrow Spaces

(Left) Infection of bone manifests itself as inflammation and necrosis of the marrow with secondary destruction of the adjacent bone. Acute inflammatory cells place this into the acute osteomyelitis category. (Right) H&E shows a large area of dead bone, with its characteristic lack of osteocytes adjacent to reactive, vital bone. The areas of vital bone with intact osteocytes can serve as an internal control against a misinterpretation of overdecalcified bone as dead bone.



Bone Death



TERMINOLOGY

Synonyms

- Osteitis

Definitions

- Osteomyelitis is inflammation or infection of bone and bone marrow
- Multiple classification schemes
 - **Composition of infiltrate**
 - **Acute:** Neutrophils
 - **Subacute:** Mix of neutrophils and chronic inflammatory cells (lymphocytes, monocytes, plasma cells)
 - **Chronic:** Chronic inflammatory cells and fibrosis
 - **Granulomatous:** Histiocytes, giant cells, and either acute or chronic inflammation
 - **Infectious agent**
 - Bacterial, fungal, viral, parasitic
 - **Method of acquisition**
 - Hematogenous (bloodstream infection spread from distant site, such as lung, urinary bladder)
 - Direct extension from contiguous site (oral cavity into jaws; mucosa into paranasal sinuses)
 - Direct contamination (broken bone, direct injury)
 - **Site of involvement**
 - Gnathic (jaw), paranasal sinuses, mastoid/temporal bone, vertebrae

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Originates as inflammation of vascularized connective tissue in bone marrow

Risk Factors

- **Injury**
 - Bone fracture or deep penetrating puncture wounds
 - Iatrogenic
 - During teeth cleaning, dental work, following surgery
 - Intravenous drug use
 - Nonsterile needles
- **Circulation limitations**
 - Diabetes, peripheral arterial disease, sickle cell disease, atherosclerosis, hypertension
- **Iatrogenic causes**
 - Indwelling urinary catheters, central lines, respirators, dialysis machines

CLINICAL ISSUES

Epidemiology

- Incidence
 - In general, uncommon disease in head and neck
 - Increased frequency of osteomyelitis in
 - Chronic systemic diseases, diabetes mellitus, poor oral hygiene, tobacco use, alcoholism, immunosuppression, malnutrition, intravenous drug abuse, malignancy
 - Gram-negative aerobic bacteria and *Candida* species more common in intravenous drug users and immunosuppressed

- Age
 - In general, all ages can be affected
 - Jaw: Usually 6th to 7th decades
- Sex
 - In general, equal gender distribution
 - Jaw osteomyelitis: Male > female

Site

- Mandible
 - Most commonly affected maxillofacial area; odontogenic infections and fractures are predisposing factors
 - Posterior body most commonly affected
 - Oral flora (usually commensal)
- Maxilla: More commonly affected in children
- Other bones: Paranasal sinuses, temporal, skull base, cervical spine

Presentation

- General findings
 - Fever, chills, irritability or lethargy, malaise, pain, headache, cranial neuropathy
 - Swelling, warmth, or redness over infected area
 - Must have high index of suspicion in patients with persistent neck pain &/or dysphagia
- Subacute or chronic type symptoms are not characteristic, making diagnosis difficult
- **Jaw**
 - Arise as complication of dental extractions and surgery, trauma, or fracture mismanagement
 - In infancy, maxilla is more commonly affected due to greater surface area and more extensive blood supply
- **Sinuses**
 - Sinusitis can lead to orbital cellulitis, subperiosteal abscess, orbital abscess, facial osteomyelitis, cavernous sinus/cortical vein thrombosis
- **Orbit**
 - More often in children, orbit is susceptible to contiguous spread from sinuses
- **Mastoiditis and skull base**
 - Starting with otitis externa ("malignant" or necrotizing), it evolves into cellulitis, chondritis, and via Haversian system, into osteomyelitis
 - Patients are usually immunocompromised: Diabetes, leukemia, AIDS, prior treatment with cytotoxic medication &/or corticosteroids
 - *Pseudomonas aeruginosa* is most frequent organism (rarely, mucormycosis, aspergillosis)
 - Must discriminate between these organisms as treatment is completely different, avoiding life-threatening outcome

Laboratory Tests

- Important to culture causative organism
- Blood cultures are often negative

Treatment

- Options, risks, complications
 - Treatment is based on causative organism, but beyond the chapter scope
 - Surgery to remove dead bone with targeted intravenous antimicrobial therapy

- Complications include osteonecrosis, septic arthritis, impaired growth, nerve paralysis (skull base), and rare development of squamous cell carcinoma (overlying draining fistula)
- Surgical approaches
 - Surgical treatment involves
 - Debridement of necrotic bone and tissue; drainage of pus/fluid
 - Obtaining appropriate culture
 - Removal of foreign objects (potential nidus for recurrent infection)
 - Achieving bone stability, including bone grafting
- Drugs
 - Drug regimens depend on organisms involved
 - Treatment usually involves extended targeted antimicrobial therapy

Prognosis

- Most cases are self-limited and cured
 - Early diagnosis and aggressive treatment is important
- Treatment for < 4 weeks has 25% relapse rate

IMAGING

Radiographic Findings

- Conventional radiographs are diagnostic from 3rd week of disease onward
- Plain films very difficult to diagnose due to anatomy

MR Findings

- Standard of care for diagnosis, without radiation exposure
- Establishes extent of disease, shows bone marrow changes and soft tissue involvement

CT Findings

- Not as useful as MR or scintigraphy

Bone Scan

- Most sensitive study (gold standard for initial diagnosis)
 - Hyperperfused inflammatory stage 2-3 days after infection starts
 - Low specificity and limited spatial resolution
 - Does not separate between osteomyelitis and bone tumors with increased bone metabolism

MACROSCOPIC

General Features

- Tend to be curettings

Size

- Range: 1-5 cm; abscesses may be larger, especially with soft tissue extension

MICROSCOPIC

Histologic Features

- Marrow fibrosis or edema is hallmark
 - Bone death assessed by marrow fibrosis and inflammation
 - Lack of osteocytes can be due to overdecalcification
- Acute
 - Neutrophilic infiltrate with delicate marrow fibrosis or edema

- Bone death and bone resorption
 - Osteoclastic resorption due to pressure of infiltrate
 - Micro-resorption due to released neutrophil neutral proteases

Subacute

- Infiltrate of both neutrophils and chronic inflammatory cells
- Bone marrow fibrosis, bone death, and resorption

Chronic

- Chronic inflammatory infiltrate and dense fibrosis
- Bone death with foci of new bone formation

Granulomatous

- Monocytoid histiocytes ± caseation (necrosis) and peripheral lymphoplasmacytic cuff

ANCILLARY TESTS

Histochemistry

- Gram, acid-fast, fluorostain, GMS, and PAS-LG (among others) highlight organisms
 - Does not give antimicrobial sensitivities

Immunohistochemistry

- Antibodies or ISH to certain infectious agents available

DIFFERENTIAL DIAGNOSIS

Inflammatory Reaction

- Inflammation part of fracture repair
- Present at tumor borders
- Lack of acute inflammation and dead bone

Lymphoma

- Atypical lymphoid infiltrate with bone remodeling and dense fibrosis
- Monoclonal immunohistochemistry reactions

Sarcoid

- Noncaseating, tight, well-formed granulomas
- Concurrent disease in lung, mediastinum, and other locations

Bisphosphonate Therapy

- Bone necrosis with death, followed by active remodeling
- More often chronic process with known medication history

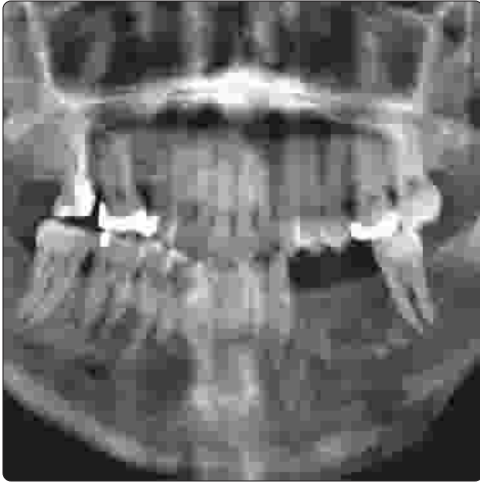
Radiation Osteitis

- Bone necrosis and death with chronic inflammation
- History usually known

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Massive Osteomyelitis of Mandible

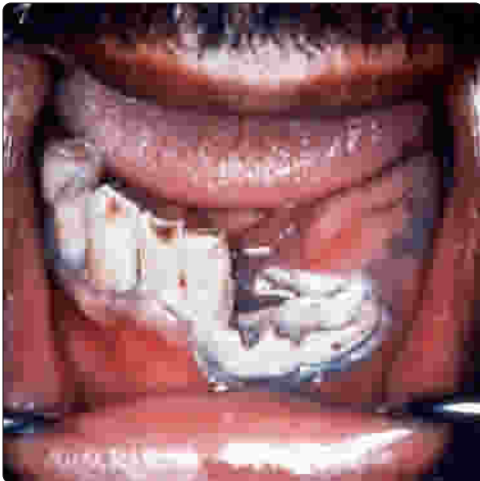


3D Reconstruction of Jaw Osteomyelitis

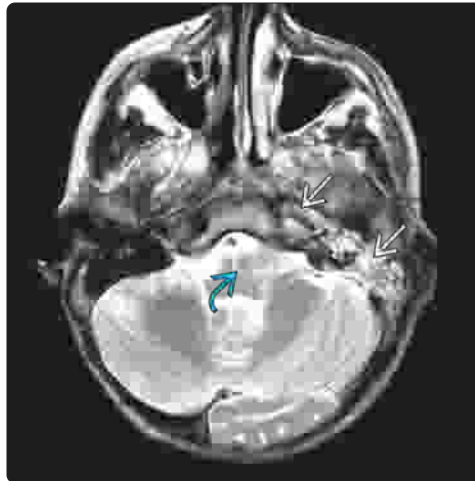


(Left) This 51-year-old man developed osteomyelitis after numerous infections involving teeth and their subsequent extractions. He had multiple other chronic systemic diseases including drug abuse, alcoholism, and diabetes mellitus. This patient, after failing more conservative treatments, eventually had his entire mandible resected. (Right) 3D reconstruction of the same patient shows the large and dramatic amount of destruction of his mandible.

Clinical Photograph of Osteomyelitis



Imaging Indicating Osteomyelitis

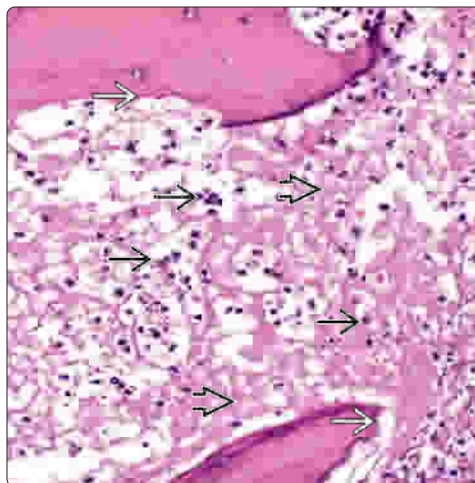


(Left) In this clinical photograph of osteomyelitis, there is destruction of the bony table with teeth loss. Poor oral hygiene and tooth decay are evident. (Right) Axial T2WI MR shows diffuse opacification of the left mastoid and petrous air cells as well as abnormal signal related to pus in the left CPA subarachnoid space. These findings correspond to increased uptake in scintigraphic studies.

Inflammatory Cells



Acute Inflammation



(Left) Chronic osteomyelitis is noted by the presence of mononuclear inflammatory cells (lymphocytes, plasma cells, macrophages) with a background of dense fibrosis. (Right) Acute inflammation is composed of neutrophils often with necrosis. Degranulation of the neutrophils releases neutral proteases resulting in bone destruction in the areas of inflammation. This bone resorption is distinct from that seen as a result of osteoclastic resorption.

KEY FACTS

TERMINOLOGY

- Fibrous dysplasia (FD) is genetically based sporadic disease that occurs in 3 clinical subtypes
 - Monostotic (1 bone); polyostotic (multiple bones); McCune-Albright syndrome (MAS)

ETIOLOGY/PATHOGENESIS

- Activating missense mutations in *GNAS* gene coding for α -subunit of stimulatory G protein is consistent finding (~85% of cases)

CLINICAL ISSUES

- Children and young adults
- Painless swelling of jaws leading to facial asymmetry, orofacial deformity, malocclusion, dental developmental disorders, bone pain, nasal obstruction, chronic sinusitis, hyperfunctioning endocrinopathies (MAS)
- Monostotic form accounts for 80-85% of cases
- Skull base > maxilla > paranasal regions

IMAGING

- Cone-beam CT is considered best technique
- Abnormal opacification, with numerous small to diffusely distributed opacities (cotton-wool, ground-glass appearances), merging with adjacent bone

MICROSCOPIC

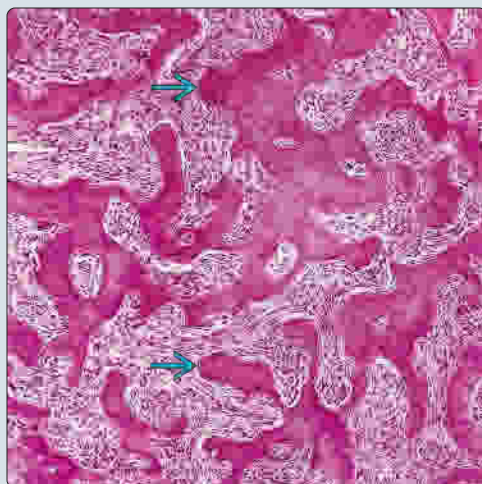
- Normal bone replaced by moderately cellular fibrous tissue
- Stroma contains fine branching, curvilinear trabeculae of woven bone
- Nearly complete lack of osteoblast rimming of bony trabeculae
- Bony spicules merge imperceptibly with adjacent cancellous bone or overlying cortex

TOP DIFFERENTIAL DIAGNOSES

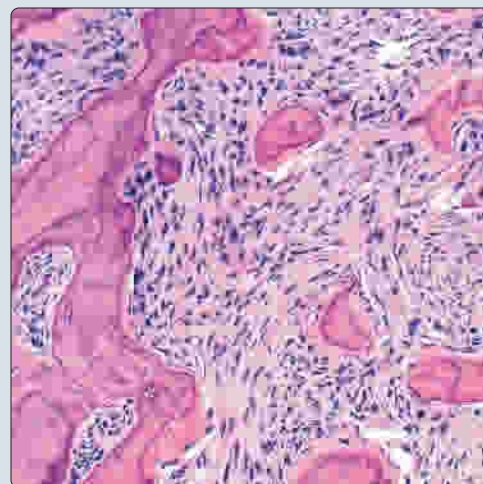
- Ossifying fibroma, osseous dysplasia, osteosarcoma, osteomyelitis (sclerosing type)

Cellular Stroma With Irregular Bone Islands

(Left) Low-power view demonstrates irregularly shaped islands and formations of woven bone with a bland, mononuclear, spindle cell background. Note the absence of osteoblastic rimming even at this magnification. (Right) There are irregular bony spicules arising straight out of the fibrous connective tissue stroma without any osteoblastic rimming.

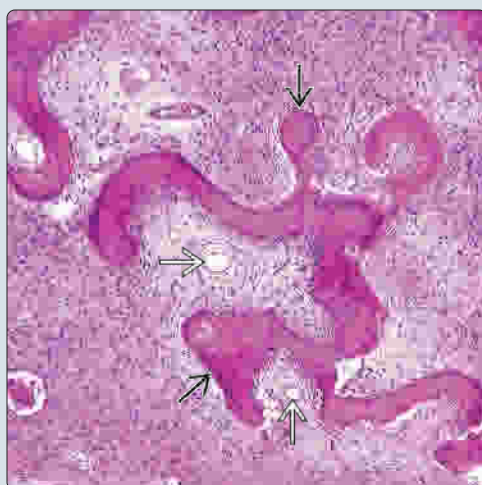


Woven Bone Spicules in Fibrous Stroma

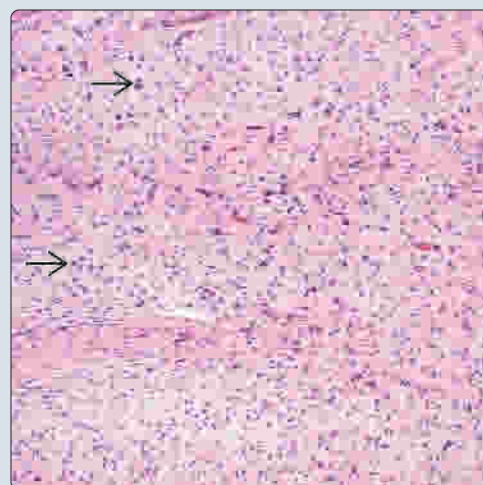


Alphabet Soup Appearance of Bone

(Left) A high-power view shows curvilinear alphabet pieces of woven bone arising directly out of the spindle cell background with small, delicate vessels. This blending without osteoblastic rimming is a helpful feature. (Right) There are no areas of bony trabecular in this field, showing only the cellular fibrous connective tissue stroma. However, rarely, tiny calcified spherules may be present in fibrous dysplasia (FD).



Calcified Spherules



TERMINOLOGY

Abbreviations

- Fibrous dysplasia (FD)

Synonyms

- Osteitis fibrosa, osteodystrophia fibrosa

Definitions

- FD is genetically based sporadic disease that occurs in 3 clinical subtypes
 - Monostotic (1 bone)
 - Polyostotic (multiple bones)
 - McCune-Albright syndrome (MAS)
 - Polyostotic FD (90%), skin hyperpigmentation (café au lait spots), and hyperfunctioning endocrinopathies (precocious puberty, fluctuating thelarche, hyperthyroidism, growth hormone excess, rickets/osteomalacia)

ETIOLOGY/PATHOGENESIS

Genetic

- Activating missense mutations in *GNAS* gene coding for α -subunit of stimulatory G protein is consistent finding (~85% of cases)
- Clonal chromosomal aberrations suggest lesion is neoplastic

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon disorder, but craniofacial bones most commonly affected
 - Incidence varies depending on monostotic vs. polyostotic cases
 - Monostotic form accounts for 80-85% of cases
 - Within severe polyostotic cases, craniofacial involvement approaches 100%
- Age
 - Children and young adults, rare in older adults
- Sex
 - Craniofacial disease shows equal gender distribution
 - Monostotic form: Equal gender distribution
 - Polyostotic form: Female > male

Site

- Craniofacial bones are typically involved in ~ 10% of patients with monostotic form and in up to 100% with polyostotic form
- Skull base is skeletal site most commonly affected
- Maxilla and paranasal regions more frequently affected than mandible
 - May be extension across suture lines to involve adjacent bones
- Term monostotic not usually employed for maxilla or face

Presentation

- Painless swelling of jaws
 - Facial asymmetry, orofacial deformity, malocclusion, dental developmental disorders, bone pain

- Maxilla swelling may lead to nasal obstruction and chronic sinusitis
- When skull base is affected, compression of cranial nerves may cause visual impairment or hearing loss
 - Craniofacial involvement can be asymptomatic and detected incidentally
- ~ 3% of patients with polyostotic form have endocrinopathies
 - MAS
 - By contrast: ~ 90% of MAS patients have craniofacial polyostotic FD lesions
- When associated with intramuscular myxomas, called Mazabraud syndrome
- Accurate classification achieved only when evaluating clinical, radiological, and histomorphological features together

Natural History

- Tendency to slow or stop disease progression after skeletal maturation
- Can cause severe deformity and asymmetry
 - Most significant: Blindness

Treatment

- Options, risks, complications
 - Treatment with bisphosphonates usually relieves pain
 - Tends not to affect natural history of disorder
- Surgical approaches
 - Generally employed to achieve cosmetic results or functional status
 - Fractures through area of FD in craniofacial bones are uncommon

Prognosis

- Considered self-limiting disease, although, after long duration of inactivity, may occasionally reactivate
- Rarely, osteosarcoma may arise

IMAGING

Radiographic Findings

- Cone-beam CT is considered best technique
 - Lower radiation dose, better accessibility and spatial resolution
- Radiographic appearance is variable based on patient age
- Craniofacial FD is poorly defined and more radiopaque, merging with adjacent bone
 - Axial FD frequently shows circumscribed radiolucency with thin sclerotic periphery
- Abnormal opacification, especially monostotic form
 - Numerous small to diffusely distributed opacities ("cotton wool")
 - Yields characteristic ground-glass or orange-skin appearance
- Early lesions may be radiolucent
 - Become increasingly radiopaque, gradually merging radiologically abnormal bone with adjacent bone
- Subclassified into 3 different patterns
 - Pagetoid (56%)
 - Cystic (21%)
 - Sclerotic (23%)
 - Preferentially involves facial bones and skull base

- o Lytic form is often in calvarial bones

MACROSCOPIC

General Features

- Gritty, nondescript fragments of bone

MOLECULAR

Activating Missense Mutations in *GNAS* Gene

- *GNAS* codes for a subunit of stimulatory G protein (Gs)
- Sporadic, congenital mutations in cAMP-regulating protein, Gs
 - o Example of somatic mosaicism in which wide spectrum of disease is possible
- Gs is central in cell signaling pathway that leads to generation of intracellular 2nd messenger, cAMP
- Activating mutations lead to ligand-independent cAMP/protein kinase A signaling
- cAMP is involved in signal transduction from multiple cell surface receptors, including
 - o Parathyroid hormone, follicle-stimulating hormone, luteinizing hormone, and thyroid-stimulating hormone
- > 90% of all mutations thus far identified involve codon 201, exon 8
 - o Arginine to histidine substitution (p.R201H, 53%) or arginine to cysteine substitution (p.R201C, 45%)
- These mutations result in inhibition of intrinsic GTPase activity of Gs protein
 - o This aspect leads to constitutive, ligand-independent generation of intracellular cAMP

MICROSCOPIC

Histologic Features

- Normal bone replaced by moderately cellular fibrous tissue
 - o Spindled fibroblasts with moderate amount of collagen
- Stroma contains fine branching, curvilinear trabeculae of woven bone
 - o Irregular shapes (alphabet soup, Chinese characters)
- Nearly complete lack of osteoblast rimming of bony trabeculae
- Bony spicules merge imperceptibly with adjacent cancellous bone or overlying cortex
- Jaw lesions may show lamellar bone
- Rarely, tiny calcified spherules may be present
- With use of polarized light, woven bone has disorganized collagen bundles
- Possible reasons for difference between maxillofacial vs. long bone FD
 - o Maxillofacial derivation from membranous bone, network of broad trabeculae
 - o Lamellar bone occurs occasionally in FD

ANCILLARY TESTS

Genetic Testing

- Detected using genomic DNA and allele-specific PCR
 - o Usually found in exon 8 of *GNAS* gene

DIFFERENTIAL DIAGNOSIS

Ossifying Fibroma

- Radiographic correlation is absolutely required
 - o Clearly demarcated lesion
 - o FD tends to be diffuse with blending into surrounding bone
- Will have bony spicules that have osteoblastic rimming, with variably cellular stroma
- Juvenile ossifying fibroma usually has more psammomatous bodies (cementicles) with areas of cystic degeneration
- Lacks *GNAS* mutation; *MDM2* amplification in up to 70% without IHC *MDM2* overexpression

Osseous Dysplasia

- Has many different types of mineralized material
- Stromal cellularity is quite variable
- Lacks woven bone trabeculae fusing to uninvolved bone
- Lacks *GNAS* mutation

Osteosarcoma (Low Grade)

- Invades through cortical bone into soft tissues
- Osteoid in background, usually with osteoblastic rimming
- Lacks woven bone trabeculae fusing to uninvolved bone

Osteomyelitis, Sclerosing Type

- Coarse trabeculae of lamellar bone
- Edematous stroma containing lymphocytes
- Lacks woven bone trabeculae fusing to uninvolved bone

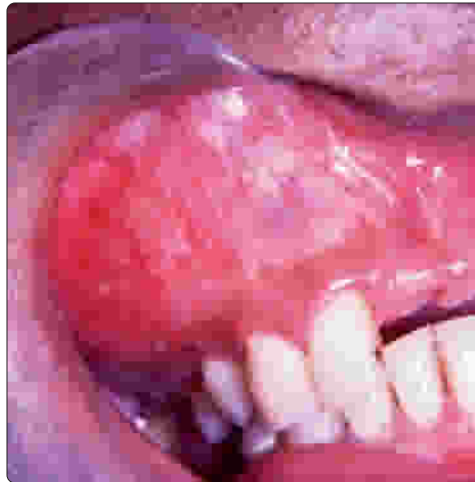
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CT With Ground-Glass Density

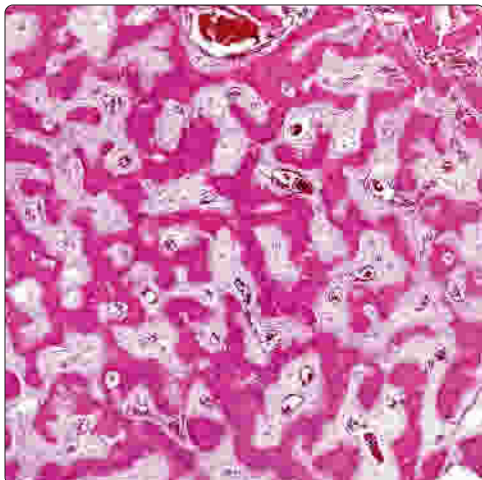


Clinical Photo of Maxilla FD



(Left) CT demonstrates expanded bone, with areas of characteristic ground-glass density with prominent cortex, interspersed with more cystic-appearing areas showing cortical attenuation. (Right) This clinical photograph shows well-developed swelling of the maxilla. In some patients, the swelling may result in significant facial deformity and malocclusion, the latter seen here.

Low-Power Alphabet Soup of FD

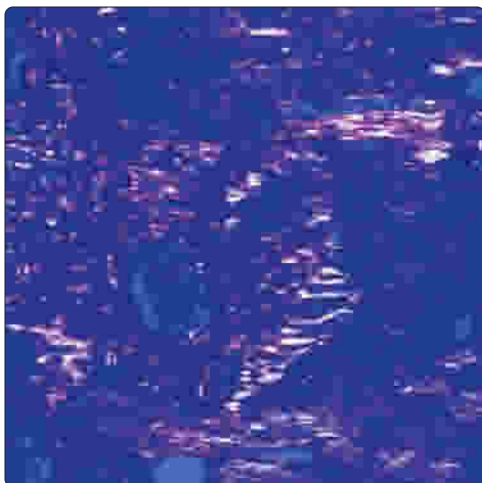


Bony Spicules Blending With Bone

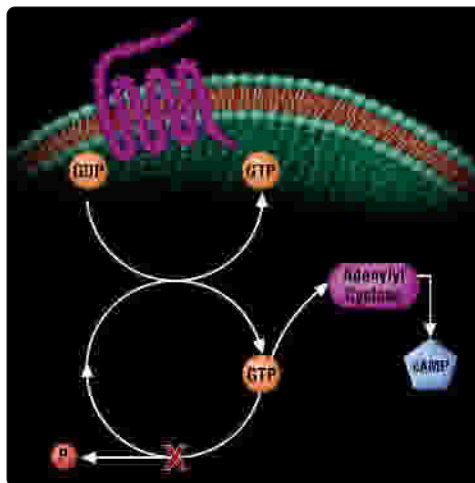


(Left) There is a sea of irregular-shaped bony spicules, giving the characteristic appearance of alphabet soup or a Chinese-character appearance. There is an absence of osteoblastic rimming. (Right) In this example of FD, the bony spicules merge imperceptibly with adjacent cancellous bone or overlying cortical bone.

Polarized View of Disorganized Bone



Graphic of Molecular Cascade



(Left) Using polarized light shows the disorganized, yellow to orange collagen bundles characteristic of woven bone. There is no order or Haversian/lamellar appearance. (Right) Mutations inactivate the intrinsic GTPase activity, preventing the inactivation of the Gs α subunit. Once activated, the mutated Gs α subunit is able to continuously stimulate adenylyl cyclase, increasing intracellular cAMP and causing continual stimulation of downstream cAMP-signaling cascades.

KEY FACTS

CLINICAL ISSUES

- Tooth-bearing areas of jaw
- Generally asymptomatic and discovered on routine dental radiographs
- Associated with vital tooth
- When patients report with symptoms, it is often in florid variant
- **Periapical** cemento-osseous dysplasia: Associated with apical areas of mandibular anterior teeth
- **Focal** cemento-osseous dysplasia: Associated with single tooth, posterior mandible is favored
- **Florid** cemento-osseous dysplasia: Multifocal involvement

IMAGING

- Mixed radiolucent/radio-opaque, lesions tend to become more dense as they mature
- Well defined with thin peripheral radiolucent rim

MACROSCOPIC

- Gross appearance is helpful in distinguishing entity from other benign fibroosseous lesions
- Gritty, fragmented, grainy pieces of bone

MICROSCOPIC

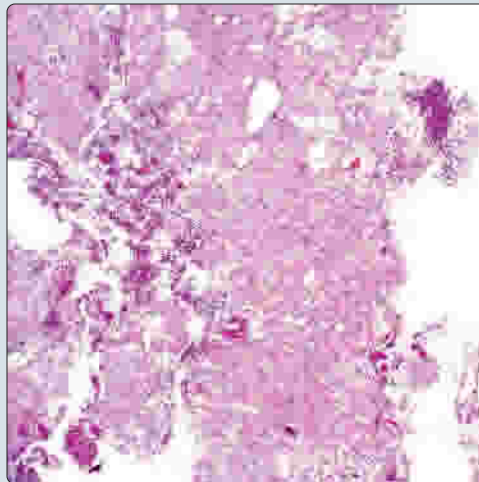
- Variably cellular fibrous stroma
- Hard tissues: Thick curvilinear trabeculae; woven bone, lamellar bone, cementum-like material
 - Advanced lesions show increased mineralization
- Osteoblastic rimming is rare
- Cavernous-like vascularity, results in artifactual free blood

TOP DIFFERENTIAL DIAGNOSES

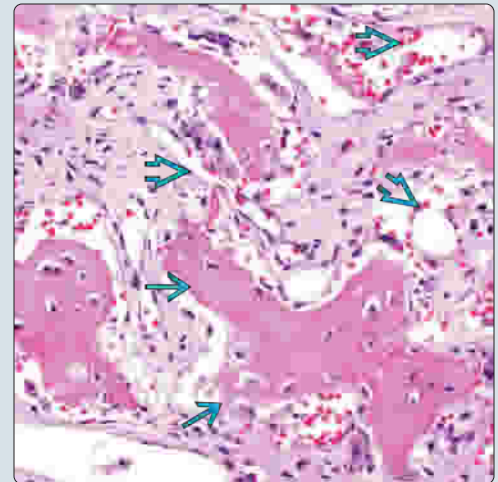
- Fibrous dysplasia
- Ossifying fibroma/active ossifying fibroma

Low-Power Histology of Cemento-Osseous Dysplasia

(Left) Low-power image demonstrates the specimen's fragmented, gritty, and hemorrhagic appearance and is reflective of its gross appearance. (Right) High-power image shows a cellular fibrous background with spindle-shaped fibroblasts. Note the small blood vessels [E] that are responsible for the free blood seen at a lower power. Within the fibrous background are spicules of bone. As the lesion matures, the bone trabeculae [E] become thicker.



High-Power Histology of Cemento-Osseous Dysplasia

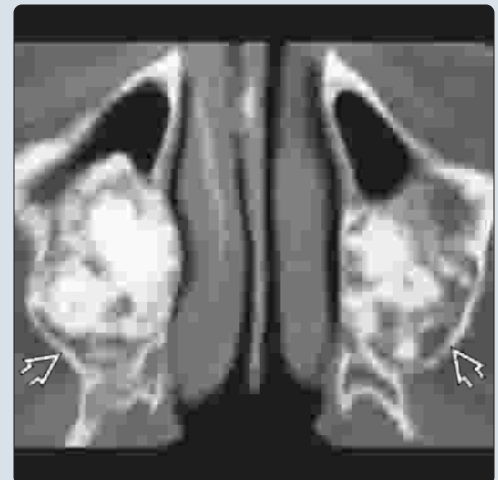


Periapical Radiograph of Focal Cemento-Osseous Dysplasia

(Left) Periapical radiograph shows a first molar affected by focal osseous dysplasia. The lesion is a mixed radiolucent, radiopaque area associated with the apex of both roots [E]. (Right) Axial CT in a patient with florid osseous dysplasia shows bilateral involvement and expansion of the posterolateral maxillary sinus borders [E]. The mature radiopaque lesions partially fill the maxillary sinuses, reducing aeration. Note the relative symmetry of the lesions.



Axial CT of Florid Cemento-Osseous Dysplasia Affecting Maxilla



TERMINOLOGY**Abbreviations**

- Cemento-osseous dysplasia (OD)

Synonyms

- Osseous dysplasia (OD)

Definitions

- Idiopathic, benign fibroosseous lesion of tooth-bearing regions

ETIOLOGY/PATHOGENESIS**Unknown**

- Likely reactive process that originates from periodontal ligament

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Frequent finding
- Age
 - Usually middle age, predilection for 3rd to 6th decades
 - Rare in patients < 20 years
- Sex
 - Female predilection
- Ethnicity
 - Predilection for blacks, reported in whites and Asians

Site

- Tooth bearing areas of jaw
 - Periapical COD: Associated with apical areas of mandibular anterior teeth
 - Focal COD: Associated with single tooth
 - Florid COD: Multifocal involvement

Presentation

- Generally asymptomatic and discovered on routine dental radiographs, associated with vital tooth
- Generally nonexpansile, some expansion may be seen in cases of florid osseous dysplasia
- When symptomatic (florid type): Pain, purulent discharge, delayed healing

Treatment

- No treatment is generally required (no surgery)
- Florid variant may need treatment for osteomyelitis

Prognosis

- Complications of osteomyelitis with bone sequestration may develop in cases of florid osseous dysplasia

IMAGING**Radiographic Findings**

- Radiolucent, radiodense, or mixed
 - Serial radiographs will show increased calcification, lesions become more dense as they mature
- Well defined with thin peripheral radiolucent rim
- Periodontal ligament appears intact and there is no fusion to tooth

MACROSCOPIC**General Features**

- Gritty, fragmented, hemorrhagic, brown, pieces of bone

MICROSCOPIC**Histologic Features**

- Variably cellular fibrous stroma with areas of storiform pattern, loose collagen
- Hard tissues: Thick curvilinear trabeculae; woven bone, lamellar bone, cementum-like material
 - Advanced lesions show increased mineralization
- Osteoblastic rimming is rare
- Cavernous-like vascularity, results in artifactual free blood
- No capsule or secondary inflammatory changes

DIFFERENTIAL DIAGNOSIS**Fibrous Dysplasia**

- Gross appearance: Tissue will often come as core or cube of bone as no distinct lesion is seen intraoperatively
- Radiographic: Ground glass or orange peel appearance; lesions blend with adjacent bone; expansile
- Site: May be seen throughout head and neck but is also found in other bones of body, maxilla > mandible
- Epidemiology: No gender or race predilection, generally 1st presents in young adults and adolescents

Ossifying Fibroma/Active Ossifying Fibroma

- Gross appearance: Often intact mass or tumor as lesion is often described as "shelling out" intraoperatively
- Radiographic: Thin radiolucent periphery may be seen; expansile; displacement of associated teeth
- Site: Gnathic bones, sinus and paranasal sinuses
- Epidemiology: Female predilection, wide age range with predilection for 3rd and 4th decades

DIAGNOSTIC CHECKLIST**Clinically Relevant Pathologic Features**

- Radiograph is generally required for accurate diagnosis

Pathologic Interpretation Pearls

- Benign fibroosseous lesions are strikingly similar, requiring clinical and radiographic correlation

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KEY FACTS

TERMINOLOGY

- **Medication-related osteonecrosis (MRON):** Avascular bone necrosis due to medications
- **Osteoradionecrosis (ORN):** Avascular bone necrosis due to irradiation

ETIOLOGY/PATHOGENESIS

- **Antiresorptive medications:** Used in treatment of osteoporosis, Paget disease, and osteotropic malignancies
 - Blocks osteoclastic activity, including osteoclastic recruitment-inhibiting bone resorption
- **Radiation injury**
 - Combination of death of osteoblasts after irradiation, failure of osteoblasts to repopulate, and excessive proliferation of myofibroblasts

CLINICAL ISSUES

- **MRON** develops in up to 7% of patients receiving IV bisphosphonates

- **MRON** reported in 0.10-0.21% of patients on long-term oral bisphosphonates
- **ORN** develops in ~ 5% of patients treated by radiation
- **MRON & ORN:** Mandible more often than maxilla
- **MRON & ORN:** May remain asymptomatic for weeks or months, and exposed bone may be presenting symptom
 - Dentoalveolar surgery common precipitating event

IMAGING

- Ill-defined mottled radiolucent/radiopaque

MICROSCOPIC

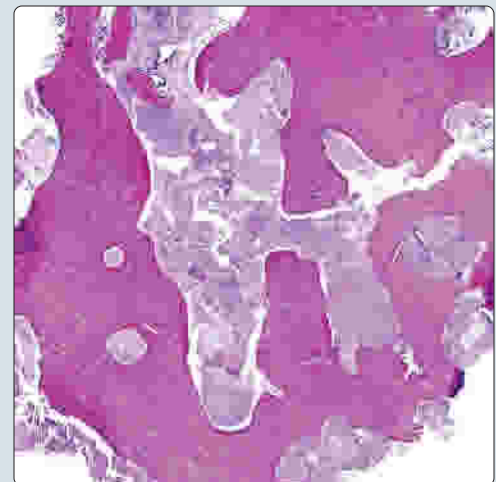
- **MRON:** Nonvital bone lacking osteocytes with scalloping pattern of resorption
 - Bacterial colonization including *Actinomyces* adjacent to bone
- **ORN:** Overlap with osteomyelitis, with histologic phase matching those of healing traumatic wounds

Bisphosphonate-Related Osteonecrosis

(Left) Medication-related osteonecrosis of the palatal torus in a patient taking bisphosphonates for low bone density shows sequestered bone with underlying granulation tissue. Treatment involves removing the sequestrum and treating the patient with topical chlorhexidine rinse. (Right) This nonviable bone lacks osteocytes within individual lacunae exhibiting resorption with adjacent colonies of bacteria organisms. Soft tissue is not always present, as in many cases the specimens received are sequestrectomies.

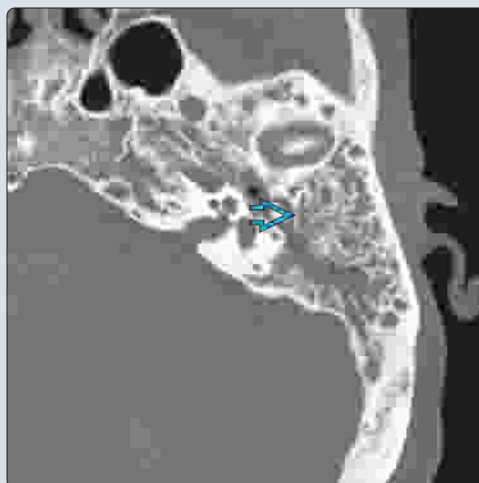


Necrotic Bone



Imaging Findings in Osteoradionecrosis

(Left) Axial CT reveals debris throughout the middle ear cleft. Examination of mastoid septations reveals coalescent changes with large defects in lateral cortex. This pattern suggests osteoradionecrosis. (Right) Lamellar trabecular bone is shown with complete marrow fibrosis and collections of bone fragments and amorphous debris. This combination of findings is quite supportive of the diagnosis of osteoradionecrosis.



Marrow Fibrosis in Osteoradionecrosis



TERMINOLOGY

Synonyms

- Medication-related osteonecrosis of jaws (**MRON**): Osteochemonecrosis, bisphosphonate-related osteonecrosis of jaws
- Osteoradionecrosis (**ORN**): Radiation osteitis, radioosteonecrosis

Definitions

- **MRON**: Avascular bone necrosis due to antiresorptive medications
- **ORN**: Avascular bone necrosis due to irradiation

ETIOLOGY/PATHOGENESIS

MRON

- **Bisphosphonates**
 - Used in treatment of osteoporosis, Paget disease, and osteotropic malignancies
 - Multiple myeloma, breast, prostate, lung, and kidney cancers
 - Blocks osteoclastic activity, including osteoclastic recruitment-inhibiting bone resorption
 - Low bone turnover can result in pathologic fractures and osteonecrosis
- **Denosumab**: Osteoclast-targeted antibody
 - Affects receptor activator of nuclear factor-κB ligand system with nonreversible deactivation of osteoclasts
 - Action is time limited and dose dependent: New osteoclasts are formed daily and are functional
- **Tyrosine kinase and vascular endothelial growth factor inhibitors**
 - Inhibit osteoclasts via osteoclastic developmental feedback loop

ORN

- Several theories
 - **Radiation injury**
 - Combination of death of osteoblasts after irradiation, failure of osteoblasts to repopulate, and excessive proliferation of myofibroblasts
 - **Trauma**: Surgical manipulation impairs healing process
 - **Infection**: Interferes with normal regenerative response
 - **Hypoxia, hypovascularity, and hypocellularity**
 - **Reactive oxygen species mediates release of cytokines**
 - **Injured endothelial cells**
 - **Release of histamine**: Damages surrounding tissues

CLINICAL ISSUES

Epidemiology

- Incidence
 - **MRON** develops in up to 7% of patients receiving IV bisphosphonates
 - Dose and duration dependent
 - Up to 4.5x more common in multiple myeloma patients than breast cancer patients
 - **MRON** reported in 0.10-0.21% of patients on long-term oral bisphosphonates

- > 5 million patients on oral antiresorptive therapy for osteoporosis
- **ORN** develops in ~ 5% of patients treated by radiation
 - No significant decrease despite improvements in preradiotherapy oral and dental care

- Age
 - **MRON & ORN**: Generally older patients
- Sex
 - **MRON**: Female > > > male when associated with osteoporosis
 - **MRON**: Female > male when associated with systemic drug therapy
 - May be reflective of use of IV bisphosphonates in breast cancer
 - **ORN**: Male > female in general

Site

- **MRON & ORN**: Mandible more often than maxilla
- **MRON**: Often in areas with thin overlying mucosa (tori)

Presentation

- **MRON**
 - Exposed bone for > 8 weeks
 - MRON may remain asymptomatic for weeks or months, and exposed bone may be presenting symptom
 - Soft tissue swelling, abscess, oral-cutaneous fistula
 - Pain
 - Loosening/mobility of teeth
 - Local factors that contribute to **MRON**
 - Dentoalveolar surgery: Tooth extraction or dental surgery common precipitating event in > 75% of cases
 - Inflammation &/or infection of soft tissue
 - Bacteria, especially *Actinomyces* species common in biopsied bone specimens
- **ORN**
 - Severe pain, trismus, mucosal ulceration
 - Exposure of necrotic bone for > 3 months
 - Local infection, often with intraoral/extraoral fistulas
 - Pathologic fractures may be seen
 - Early lesions may be asymptomatic
 - Despite seeing exposed devitalized bone through ulcerated mucosa or skin
- Factors that may contribute to development of **ORN**
 - Size and site of primary tumor treated by radiation
 - Dose of radiation
 - Less common after hyperfractionated radiotherapy at 72–80 Gy
 - Rare with < 60 Gy of radiation exposure
 - More common when brachytherapy is used
 - When chemotherapy is added to radiotherapy, incidence of ORN may be increased
 - Interval between radiotherapy and onset of ORN can vary, usually 4-24 months
 - Type of mandibular resection, injury, or dental extractions
 - Mainly as result of injury from extractions and infection from periodontal disease

Treatment

- Options, risks, complications

- **MRON**
 - Conservative surgical technique
 - Odontogenic infections treated aggressively
 - Endodontic therapy preferable to tooth extraction
- **ORN** irreversible and extremely difficult to treat
 - Several different approaches
 - Conservative management (only indicated in small necrotic bone areas)
 - Invasive surgery
 - Hyperbaric oxygen therapy
- Surgical approaches
 - Variable surgical approaches
 - Simple sequestrectomy to hemimandibulectomy
 - Sequestrectomies should be delayed until necrotic bone can be lifted free easily
 - Leaves delicate granulation tissue in bed undamaged
 - Unless radical resection is planned, surgery should be designed to create as little trauma to bone as possible
 - Healing will often be problematic without measures to improve vascularity
- Osteoclasts may be short distance from bone interface: Floating position
- Soft tissue, if present, shows mostly acute inflammation, chiefly neutrophils
- Bacterial colonization adjacent to bone
 - Actinomycotic colonies along with mixed bacteria
- **ORN**
 - Overlap with osteomyelitis
 - Histopathological phases closely resemble healing of traumatic wounds
 - 3 distinct phases are seen
 - **Initial prefibrotic** phase
 - Changes in endothelial cells predominate with associated inflammatory response
 - **Constitutive organized** phase
 - Abnormal fibroblastic activity predominates with disorganization of extracellular matrix
 - **Fibroatrophic** phase
 - Tissue remodeling occurs
 - Sclerotic bone with empty osteocyte lacunae
 - Reactive, metaplastic squamous mucosa may line fistula

Prognosis

- **MRON**: Prevention is considered best treatment
 - Need to have accurate assessment of continuous total drug-exposure history to determine risk
 - Therapy not always continuous
- **ORN**: Risk remains for life, albeit to lesser degree
 - Progression can lead to pathologic fracture
 - Outcome often based on reason for radiation
 - Symptoms may never be completely eliminated

IMAGING

Radiographic Findings

- **MRON**: Relatively nonspecific
 - Panoramic radiographs demonstrate localized or diffuse osteosclerosis
 - Little or no ossification at prior extraction site
 - CT findings more sensitive than plain film
 - Helpful in delineating disease extent
 - Demonstrates focal sclerosis and early sequestrum formation
 - Nuclear imaging findings
 - May have utility as predictive tool but limited value in patients with existing disease
- **ORN**
 - Panoramic radiographs demonstrate osteolysis
 - Show typical ill-defined mottled pattern
 - Radiolucent areas alternating with radiopaque areas
 - MR findings
 - Low signal intensity on T1WI
 - Postcontrast T1WI shows contrast enhancement
 - Variable T2 signal intensity

MICROSCOPIC

Histologic Features

- **MRON**
 - Nonvital bone lacking osteocytes with scalloping pattern of resorption

DIFFERENTIAL DIAGNOSIS

Recurrent Carcinoma

- If radiation was given for squamous cell carcinoma, atypia in squamous-lined fistula may be worrisome
- Squamous epithelium immediately associated with granulation tissue and necrotic bone favor fistula

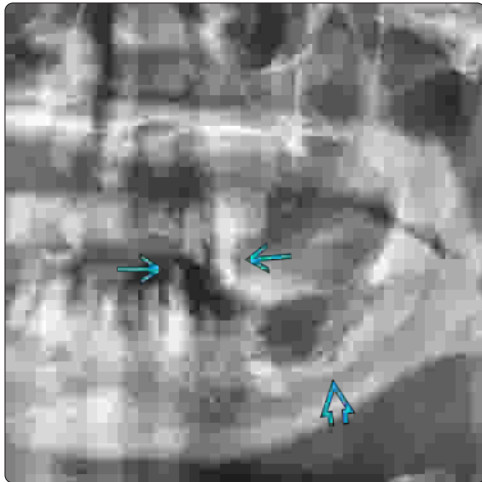
Radiation Changes

- Cytologic atypia from radiation changes can also mimic malignancy
- Fibroblastic, endothelial, and squamous epithelia all affected by radiation
- History will generally help to make separation

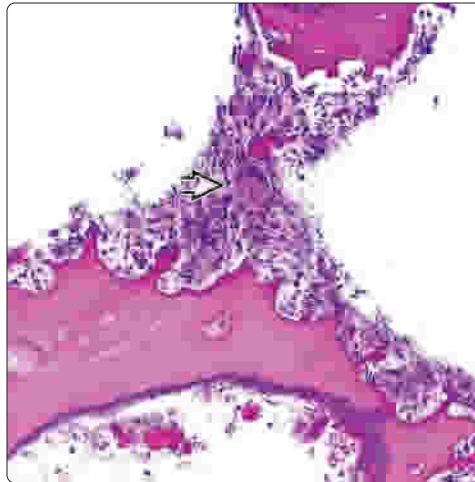
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Osteoradionecrosis of Mandible

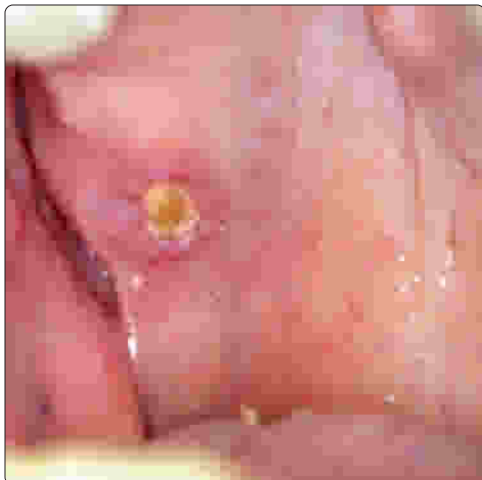


Radiation Necrosis of Mandible

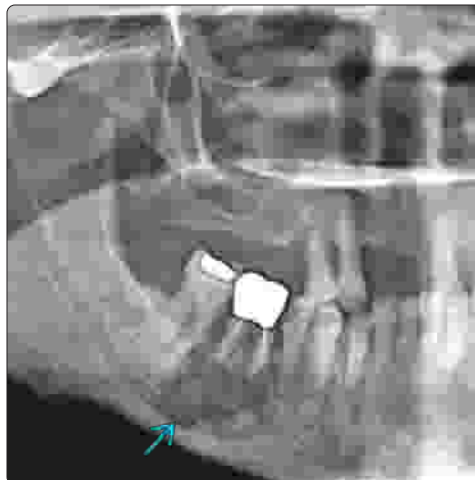


(Left) A 58-year-old man status post chemoradiation therapy for oropharyngeal carcinoma presented with a mottled mixed radiolucent radiopaque lesion in the mandible [1]. The patient had poor dental health as evidenced by the numerous caries and broken down teeth [2], which is a risk factor for the development of osteoradionecrosis. (Right) The bone is necrotic, lacking nuclei within the lacunar spaces. Mostly chronic inflammation is present in the granulation tissue containing a giant osteoclast [3].

Bone Sequestrum: Antiresorptive Therapy

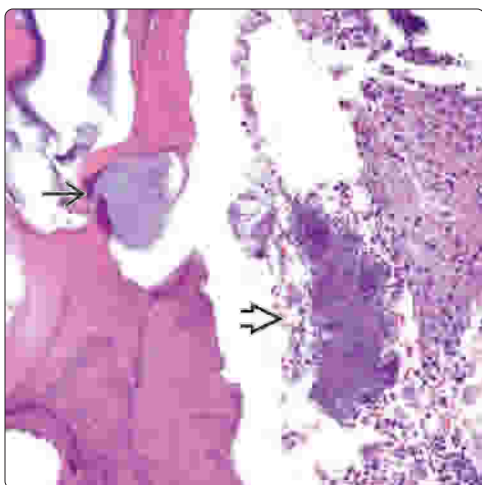


Bisphosphonate-Related Osteonecrosis

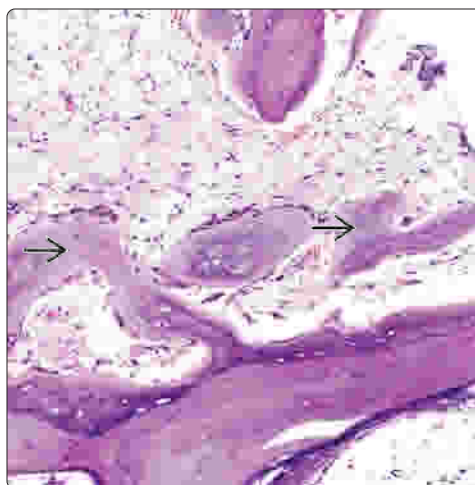


(Left) A 68-year-old man treated with zoledronic acid for metastatic lung carcinoma developed an area of exposed necrotic bone in the maxillary tuberosity. (Right) A 56-year-old woman treated with zoledronic acid for breast carcinoma presented with an ill-defined radiolucent area at the apex of the first molar [1]. Initially thought to represent periapical disease, the lesion did not improve after endodontic therapy. No evidence of metastatic breast carcinoma was present in the biopsy.

Bisphosphonate Necrosis: Actinomycosis



New Bone Formation



(Left) Bone sequestrum and associated soft tissue from the lingual tori of a patient on oral bisphosphonates for low bone density shows both actinomycotic colonies [1] and mixed bacterial colonies [2] present adjacent to the bone. Granulation tissue containing mostly neutrophils is present. (Right) Later in the repair stages of radiation osteitis, new bone formation [3] can be noted around the nonviable trabeculae. Reversal lines may be quite prominent. There is often associated scattered chronic inflammation, helping to confirm the diagnosis.

KEY FACTS

TERMINOLOGY

- Paget disease of bone is localized skeletal disorder characterized by osteoclasts of increased number and size containing multiple nuclei

CLINICAL ISSUES

- Occurs in familial clusters
- Usually seen in patients over age of 40
- Can be monostotic or polyostotic
- Biochemical markers of bone turnover (alkaline phosphatase) are key in disease monitoring
- Oral bisphosphonates are mainstay of therapy

IMAGING

- Plain films: Blade of grass sign
- Typical cotton wool or ground-glass appearance
- Late stages: Predominantly sclerotic

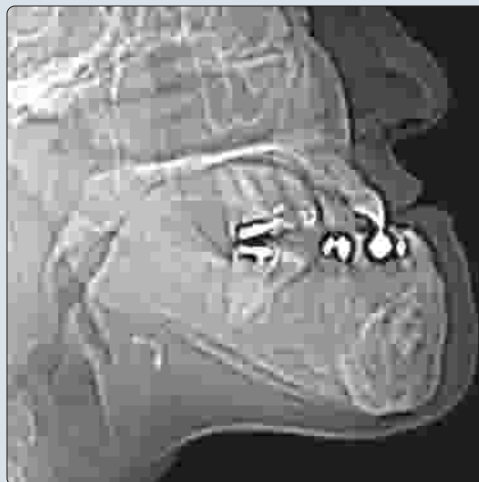
MICROSCOPIC

- Affected bones will have enlarged pumice-like gross morphology
- Mid-stage: Osteoblastic and osteoclastic activity
 - Osteoclasts are larger in size and have large number of nuclei
- Numerous reversal lines are noted as result of increased remodeling
- High degree of vascularity noted in intervening intertrabecular spaces
- Initially, osteoporosis predominates

TOP DIFFERENTIAL DIAGNOSES

- Renal osteodystrophy
- Hyperparathyroidism
- Ossifying hemangioma

Enlarged Mandible of Paget Disease

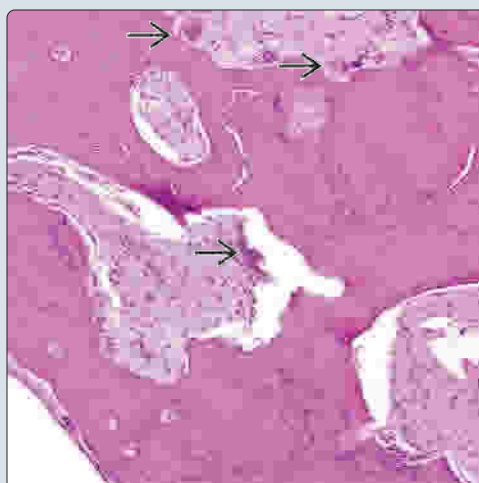


(Left) Lateral scanogram shows Paget disease of the mandible. The mandible is enlarged, and there is a discrepancy in the size of the mandible vs. maxilla and an anterior crossbite. (Right) H&E section shows bone with irregular, scalloped edges with multiple reversal lines and osteoclasts. This change can be seen in other disorders and thus requires radiographic correlation.

Multiple Reversal Lines in Paget Disease

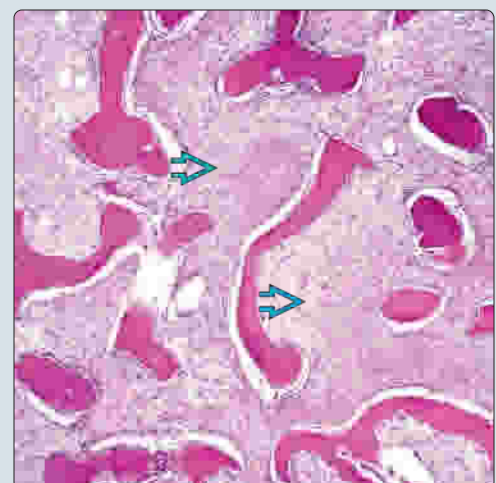


Numerous Osteoclasts



(Left) H&E demonstrates thickened trabecular struts of bone with prominent reversal lines. There are numerous osteoclasts, while osteoblasts are not as commonly present. (Right) While the early and middle stages of Paget disease show a lot of osteoblastic and osteoclastic activity, the end stages are less active and are characterized by sclerosis and fibrotic marrow.

End-Stage Paget Disease



TERMINOLOGY

Synonyms

- Osteitis deformans

Definitions

- Paget disease of bone is localized skeletal disorder characterized by osteoclasts of increased number and size containing multiple nuclei
 - Excessive breakdown and formation of bone tissue
 - Named after Sir James Paget, who initially described disease in 1877

ETIOLOGY/PATHOGENESIS

Infectious Agents

- No conclusive proof for infectious agent, although proposed based on electron microscopy data

CLINICAL ISSUES

Epidemiology

- Incidence
 - Occurs in familial clusters and sporadically
 - 15-40% of patients have positive family history
 - Nongenetic factors are also involved in disease presentation
 - Variable penetrance in families
 - Highly localized nature of disease
 - Epidemiologic data over past 25 years
- Age
 - Usually seen in patients over age of 40 years
 - Estimated that 1 in 100-150 individuals over age of 45 years has Paget
- Sex
 - Equal gender distribution
- Ethnicity
 - Asian populations tend to be less commonly affected

Site

- Can affect any bones
 - Monostotic: 1 bone
 - Polyostotic: Multiple bones
- Most common sites are
 - Pelvis (70%), femur (55%), lumbar spine (50-55%), **skull** (40%), tibia (30%)
 - Feet, hands, and **facial** bones are rarely affected but are seen in some patients

Presentation

- Tends to be nonspecific
- Disease weakens bones
- Results in number of symptoms
 - Bone pain is most common (often joint associated)
 - Headaches, hearing loss
 - Drowsiness due to vascular steal syndrome
 - Deformities: Increased head size, change in curvature of spine, changes in vision if orbits are affected
 - Fractures
 - Arthritis: Joint cartilage damage

- Teeth spread: Muscles pull abnormally on bone, resulting in intraoral displacement of teeth, malocclusion, and chewing difficulties
- Teeth may show hypercementosis (increased cementum deposition at tooth root)
- Cardiovascular disease is common
- Kidney stones are more common
- Central nervous system affected by pressure of bone on brain, spinal cord, and nerves

Laboratory Tests

- Biochemical markers of bone turnover are key in monitoring disease progression and response to therapy
- Total serum alkaline phosphatase (ALP) may be useful in monitoring the disease
 - Elevated in over 85% of Paget patients
- Serum calcium, phosphorous, and aminotransferase are normal in Paget

Natural History

- Excessive osteoclastic activity in Paget disease causes accelerated bone resorption
- Tightly coupled to recruitment of osteoblasts in that area
- Result is rapid formation of disorganized bone tissue that is mechanically weaker than native bone
 - Fractures and deformity result
- High output cardiac failure in some patients
 - High vascularity in lesions can sequester large amounts of circulating blood in larger bones
- Low percentage of patients can develop secondary sarcoma
 - Osteosarcoma, undifferentiated pleomorphic sarcoma, fibrosarcoma, giant cell tumor of bone
 - Secondary sarcomas are generally high grade

Treatment

- Options, risks, complications
 - Bisphosphonates are one of mainstays
 - Osteonecrosis can be complication of this therapy
 - Risk of fracture remains high
 - Calcium and vitamin D supplementation to manage osteoporosis
 - Must be used with caution in bisphosphonate therapy and kidney stone patients
 - Risk of secondary sarcoma is 4-10%
- Surgical approaches
 - Joint replacement can be difficult due to underlying abnormal bone
 - Fracture repair is often difficult due to underlying nature of bone
 - Oncologic surgery needed with secondary sarcomas
- Drugs
 - Oral bisphosphonates are most widely prescribed agents for Paget disease
 - Use may be limited by complicated dosing requirements and poor gastrointestinal absorption
 - Drug therapy regimens can result in mandibular osteonecrosis in some cases
 - Calcitonin analogues are infrequently used

Prognosis

- Poor prognosis with secondary sarcoma

- Undifferentiated pleomorphic sarcoma and osteosarcoma most common secondary sarcomas
- High-output cardiac failure difficult to manage

IMAGING

Radiographic Findings

- Initial work-up should include skeletal survey and bone scan
- Initial presentation on plain films will show osteoporosis
- Affected bones will be enlarged and thickened
- Plain films will often show blade of grass sign as initial presentation
 - Caused by advancing waves of osteoclasts resorbing bone along long axis of bone
- As disease progresses, typical cotton wool or ground-glass appearance is noted
 - Appearance due to presence of osteoblasts synthesizing osseous matrix
- Late stages of disease are predominantly sclerotic
- Dental radiographs show loss of lamina dura, hypercementosis, and calcified pulp chambers

Bone Scan

- Intense uptake of tracer at affected sites
 - Due to increased metabolic activity from osteoblastic activity
 - Useful in identifying polyostotic involvement

MACROSCOPIC

General Features

- Affected bones will have enlarged pumice-like gross morphology
- Bone can be grossly friable

Sections to Be Submitted

- 1 per centimeter if sarcoma is involved

Size

- Variable depending on bone involved

MICROSCOPIC

Histologic Features

- Findings reflect stage of disease
 - **Initial** stage: Reflective of osteoclastic activity
 - Numerous osteoclasts
 - Increased vascularity
 - Numerous resorptive surfaces
 - **Mid** stage: Mix of patterns
 - Osteoclastic resorption
 - Increased vascularity
 - Numerous surfaces covered with active osteoblasts
 - **End** stage: Primarily sclerotic
- Osteoclasts are larger in size and have large number of nuclei
- Numerous reversal lines are noted as result of increased remodeling
- High degree of vascularity noted in intervening intertrabecular spaces
- Initially osteoporosis predominates
- Middle stage reveals both osteoblastic and osteoclastic activity

- As disease becomes less active, marrow appears fibrotic

ANCILLARY TESTS

Histochemistry

- Alkaline phosphatase staining in osteoblasts in these specimens

Genetic Testing

- Familial cases display autosomal dominant pattern of inheritance with variable penetrance
- Studies of families with Paget have identified several loci
 - 2q36; 5q31; 5q35; 10p13; 18q22, 13, 14; sequestosome 1 (*SQSTM1*) gene on chromosome 5

DIFFERENTIAL DIAGNOSIS

Renal Osteodystrophy

- High osteoclastic activity due to secondary hyperparathyroidism
- Low intervening vascularity
- Marked increase in osteoid seam production
- Paratrabeular fibrosis often noted
- High percentage of resorptive surfaces without reversal lines
- Mosaic morphology usually not noted

Hyperparathyroidism

- Increased number of osteoclasts
- Increased resorptive surfaces

Ossifying Hemangioma

- Variable amounts of delicate, well-formed vessels
- Small area involved rather than larger areas of Paget
- Bone forms in thin boundaries around vessels
- Mosaic pattern unusual

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Need to see constellation of clinical and pathological signs
- Radiology key to interpreting biopsy specimens
- Need to rule out forms of hyperparathyroidism before diagnosis
- Reversal lines in bone present in a number of diseases
- Any presence of atypia should be followed up to rule out secondary sarcoma

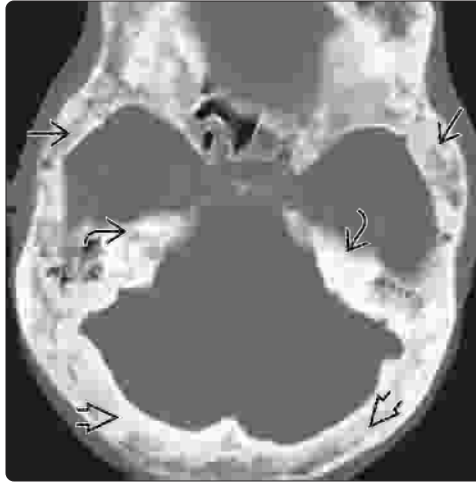
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Misshapen Bones of Skull



CT of Skull With Paget Disease



(Left) This graphic represents a patient with Paget disease involving multiple bones of the head. The bones are misshapen and widened. The bones have a gross appearance resembling the porosity of volcanic or pumice stone. (Right) Axial bone CT shows mixed-phase Paget disease involving the entire calvaria and cranial base. There is diffuse cotton wool appearance of the squamous temporal bone and the occipital bone.

Radiograph of Mandibular Expansion



Radiograph of Hypercementosis



(Left) Axial bone CT in a patient with Paget disease shows the mandible is expanded, and there is no apparent periodontal ligament space around the tooth roots. (Right) Periapical radiograph in a patient with Paget disease shows hypercementosis of the right 2nd mandibular molar tooth roots and alteration of laminae dura to the Pagetic bone pattern. The periodontal ligament spaces are narrowed or absent.

Osteoclasts and Osteoblasts



Large Osteoclasts



(Left) This image shows extensive woven bone with numerous osteoclasts and active osteoblasts from the middle stage of Paget disease. Reversal lines are present but are not as prominent as some cases. These changes are nonspecific. Clinical and radiographic correlation are required. (Right) The osteoclasts in Paget disease are larger than normal osteoclasts and increased number of nuclei. Numerous osteoclasts are a feature of the initial and mid stages of Paget disease.

KEY FACTS

TERMINOLOGY

- Potentially locally aggressive osteolytic lesion of gnathic bones

CLINICAL ISSUES

- Favors mandible
- Surgical curettage, rarely resection for large aggressive lesions
- Alternative treatments: Corticosteroid, calcitonin, and interferon- α
- Commonly recur
- Uncommon
- Wide range
- Female > male (2:1)

IMAGING

- Radiolucent defect: Unilocular or multilocular
- Expansile

MACROSCOPIC

- Friable, brown, and hemorrhagic



MICROSCOPIC

- Giant cells
 - Most likely related to osteoclasts
 - Few to upward of 20 nuclei
- Stroma
 - Loosely arranged to fibrous
 - Cellular
 - Erythrocyte extravasation with hemosiderin

TOP DIFFERENTIAL DIAGNOSES

- Brown tumor of hyperparathyroidism
- Cherubism
- Aneurysmal bone cyst
- Giant cell tumor
- Peripheral giant cell granuloma

CT of Maxilla Central Giant Cell Lesion


(Left) CT shows a well-delineated and expansile lesion . (Right) Intraoperatively, giant cell lesions are often described as hemorrhagic, red-brown and friable . A small incisional biopsy was performed due to concerns about bleeding. After the initial diagnosis of a giant cell lesion, a brown tumor of hyperparathyroidism was ruled out and the patient was transferred to a large medical center for definitive treatment.

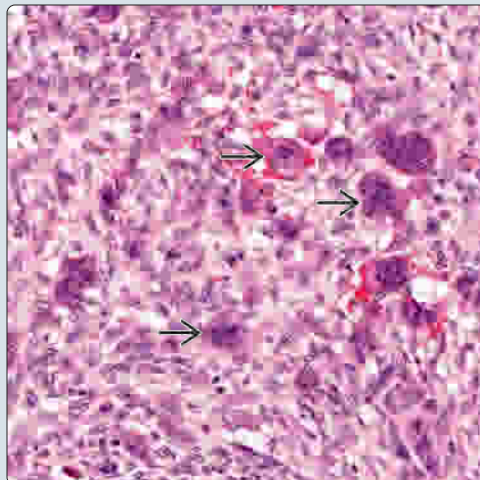


Intraoperative Photo of Tumor

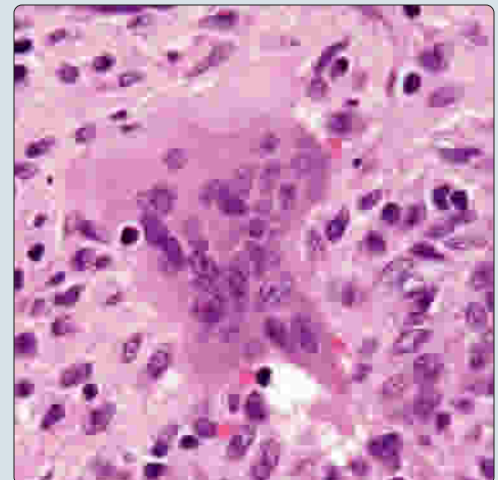


Multiple Osteoclastic-Type Giant Cells

(Left) Hematoxylin and eosin shows numerous multinucleated giant cells associated with red blood cell extravasation. The nuclei of the multinucleated giant cells  are similar to those of the stroma. This tumor shows loose stroma, however, the stroma may vary among lesions or even be variable in the same tumor. (Right) Hematoxylin and eosin shows the variability in size and shape of the giant cells within a giant cell lesion. Some cells may have upwards of twenty nuclei per cell.



Multiple Nuclei With Giant Cell



TERMINOLOGY

Synonyms

- Central giant cell granuloma, giant cell tumor, giant cell reparative granuloma

Definitions

- Potentially locally aggressive osteolytic lesion of gnathic bones

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Controversial: Neoplastic vs. reactive
 - Aggressive vs. nonaggressive; reactive is not favored

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon
- Age
 - Wide range, peak in mid to late teens
- Sex
 - Female > male (2:1)

Site

- Mandible more commonly affected
 - More common in anterior region
 - Frequently crosses midline

Presentation

- Nonaggressive
 - Asymptomatic, detected on routine dental radiographs
 - Few symptoms: Slow growing, painless expansion of bone
- Aggressive
 - Pain &/or paresthesia
 - Erosion of cortical plates, resorption of adjacent roots, and tooth displacement

Treatment

- Surgical approaches
 - Curettage
 - Rarely resection for large aggressive lesions, with reconstruction
- Drugs
 - Corticosteroid (such as triamcinolone): Weekly injections into lesion
 - Calcitonin: Subcutaneous injection or nasal spray
 - Interferon- α injections

Prognosis

- Commonly recur

IMAGING

Radiographic Findings

- Expansile, radiolucent defect: Unilocular or multilocular
- Well delineated, but may resorb teeth roots
- Occasionally crosses midline of jaw

MACROSCOPIC

General Features

- Friable, brown, and hemorrhagic

MICROSCOPIC

Histologic Features

- Giant cells
 - Most likely related to osteoclasts
 - Focal collections to diffuse distribution
 - Variable size and shape, with up to 20 nuclei per cell
- Stroma
 - Cellular, loosely arranged to fibrous
 - Erythrocyte extravasation with hemosiderin
- Correlation of histology with aggressive nature
 - Debatable, with mixed results
 - Cellular stroma, uniformly distributed giant cells with increased mitotic figures (not atypical)

ANCILLARY TESTS

Genetic Testing

- No mutations of *SH3BP2* gene (known to cause cherubism), making this a distinct entity

DIFFERENTIAL DIAGNOSIS

Brown Tumor of Hyperparathyroidism

- Signs and symptoms of parathyroid dysfunction
- Serum calcium and parathyroid hormone levels abnormal

Cherubism

- Distinctive clinically; familial; manifests in early childhood with bilateral jaw involvement

Aneurysmal Bone Cyst

- More cystic and more hemorrhagic

Giant Cell Tumor

- Believed to occur exclusively in long bones

Peripheral Giant Cell Granuloma

- Common proliferation of multinucleated giant cells caused by trauma or irritation, exclusive to gingiva or alveolar ridge
- Does not affect bone (i.e., not central)

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KEY FACTS

TERMINOLOGY

- Benign empty or fluid-filled cavity in bone

ETIOLOGY/PATHOGENESIS

- Controversial, although unknown
- Trauma (reported infrequently)

CLINICAL ISSUES

- Common lesion, affecting males in first 2 decades
- Most are asymptomatic
- Mandible, specifically premolar-molar region
- Male > female
- Open cavity to confirm biopsy
- Curettage of bony wall

IMAGING

- Radiolucent
- Defect often shows "scalloping" between tooth roots

MACROSCOPIC

- Clinically, empty or containing blood or straw-colored fluid
- Scant fragments of friable soft tissue
- Range: 1-10 cm

MICROSCOPIC

- Small fragments of fibrovascular connective tissue
- Small fragments of bone
- No epithelial lining

TOP DIFFERENTIAL DIAGNOSES

- Developmental odontogenic cysts
 - Dentigerous cyst
 - Lateral periodontal cyst
- Reactive odontogenic lesions
 - Radicular cyst (periapical cyst)
 - Periapical granuloma

Intraoperatively Empty Cavity

(Left) Knowledge of the inoperative appearance is essential to the accurate diagnosis of a simple bone cyst. Without an intraoperative description or a radiograph, the focus of the histologic diagnosis may erroneously fall on the bony window that is often times submitted with the characteristically scant specimen. (Right) A well-defined radiolucency in the mandibular molar-premolar region is highly characteristic of a simple bone cyst.

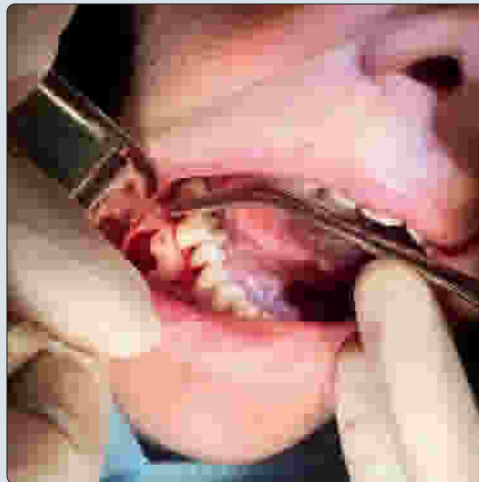
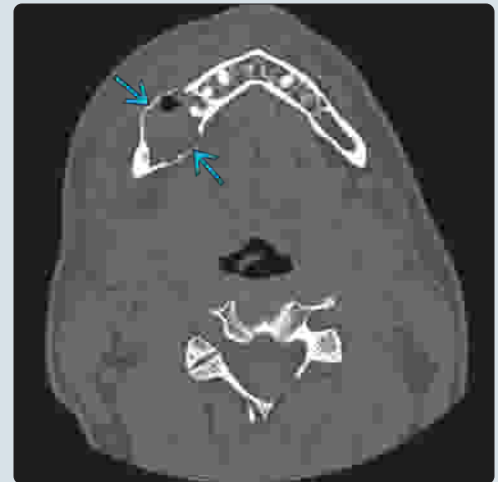
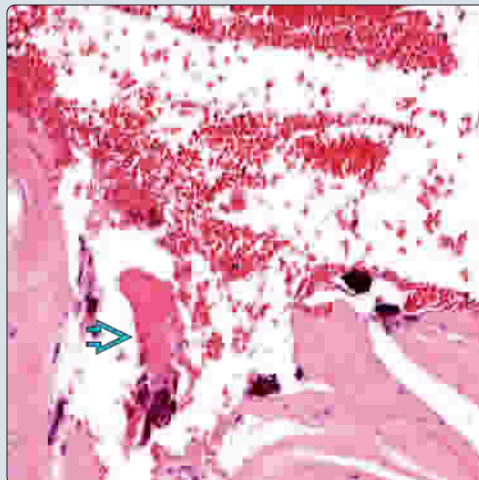


Image Study of Simple Bone Cyst



Scant Connective Tissue

(Left) Intraosseous nonepithelial-lined cyst includes scant fibrovascular connective tissue, numerous red blood cells, and detached fragment of bone. Because of the lack of tissue for histologic review, an accurate gross description is helpful to alleviate the concern for a possible loss of tissue during processing. (Right) This photomicrograph shows loose fibrovascular connective tissue that was curetted from the walls of the essentially empty bony cavity. An area of dystrophic calcification is present in the soft tissue.



Dystrophic Calcification



TERMINOLOGY**Synonyms**

- Traumatic bone cyst, traumatic bone cavity, solitary bone cyst, hemorrhagic cyst

Definitions

- Benign empty or fluid-filled cavity within bone

ETIOLOGY/PATHOGENESIS**Pathogenesis**

- Controversial, although unknown
- Trauma (reported infrequently)
 - Causes intraosseous hematoma
 - Hematoma fails to involute resulting in cyst/cavity
- Disturbance in bone growth
- Vascular anomalies
- Result of low-grade infection

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Common
- Age
 - Found primarily in first 2 decades of life
- Sex
 - Male > female

Site

- Mandible
 - Premolar-molar region
- Lesions of maxilla are rare

Presentation

- Most are asymptomatic
 - Discovered with routine dental radiographs
- Pain and swelling
- Sensitivity of nearby teeth; teeth test as vital
- Expansion is not uncommon
- Rare: Paresthesia; pathologic fracture

Treatment

- Surgical approaches
 - Open cavity to confirm biopsy
 - Curettage of bony wall
 - Large lesion may require bone graft

Prognosis

- Recurrence may develop
 - Tends to be higher if there are multiple cysts
 - Usually develops within 3 years, if it is going to recur

IMAGING**Radiographic Findings**

- Well-defined radiolucency
- Defect often shows scalloping between tooth roots
 - 50% of cases
- Rarely, multifocal
- Rarely, associated with benign fibroosseous lesion
 - Cementoosseous dysplasia

MACROSCOPIC**General Features**

- Clinically, empty or containing blood or straw-colored fluid
- Scant fragments of friable soft tissue
- Small bone fragments
- Larger bone fragments
 - May represent bone removed to gain access to cavity, creating bone window

Size

- Range: 1-10 cm

MICROSCOPIC**Histologic Features**

- Small fragments of fibrovascular connective tissue
- Small fragments of bone
 - Reactive with cellular trabeculae
- Red blood cells
- Rare giant cells
- No epithelial lining
- Dystrophic calcifications

DIFFERENTIAL DIAGNOSIS**Developmental Odontogenic Cysts**

- Dentigerous cyst
 - Associated with crown of unerupted tooth
 - Cyst lining
- Lateral periodontal cyst
 - Associated with lateral aspect of tooth root
 - Cyst lining

Reactive Odontogenic Lesions

- Radicular cyst
 - Cyst lining
 - Associated with root of nonvital tooth
- Periapical granuloma
 - Dense inflammatory infiltrate
 - Associated with root of nonvital tooth

DIAGNOSTIC CHECKLIST**Clinically Relevant Pathologic Features**

- Radiolucent "scalloping" between tooth roots

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KEY FACTS

TERMINOLOGY

- Developmental cyst surrounding crown of impacted tooth and attached to cementoamel junction

CLINICAL ISSUES

- Most common developmental cyst
- Peak incidence: 2nd-3rd decades (mean: 33 years)
- Male predilection: Male > female (1.7:1)
- Most commonly associated with mandibular 3rd molars or maxillary canines
- Expansion of bone with pain
- Resorption of adjacent teeth
- Treated by careful enucleation of cyst

IMAGING

- Usually unilocular radiolucency around crown of affected tooth, with well-defined sclerotic border
- Relationship to tooth
 - **Central:** Surrounds crown of tooth

- **Lateral:** Cyst grows laterally along root and partially surrounds crown
- **Circumferential:** Surrounds crown and much of root

MICROSCOPIC

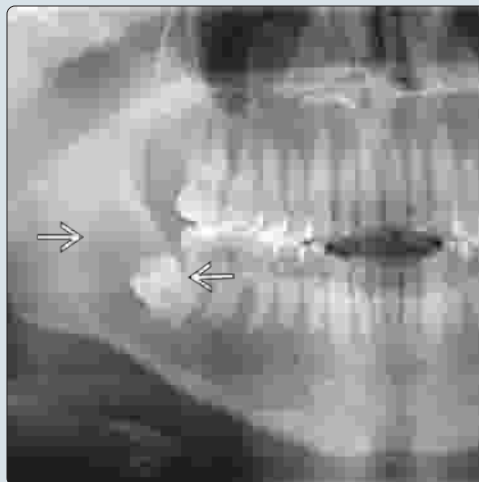
- Noninflamed: 2-3 layers of cuboidal cells, with occasional mucus or ciliated cells
- Inflamed: Proliferative or hyperplastic epithelium with rete ridges and chronic inflammatory cells
- Fibrous connective tissue

TOP DIFFERENTIAL DIAGNOSES

- Enlarged dental follicle
- Glandular odontogenic cyst
- Unicystic ameloblastoma

Panorex of Dentigerous Cyst

(Left) This orthopantomograph shows a misplaced mandibular 3rd molar (#32) with a radiolucent unilocular cyst originating near the crown-root junction and surrounding the tooth crown ➡. (Right) Gross photograph shows the crown of the tooth within the cyst. The cyst wall is attached to the tooth at the cementoamel junction ➡ and forms a collar. This feature is seldom preserved, unless the sample is carefully removed and dissected.

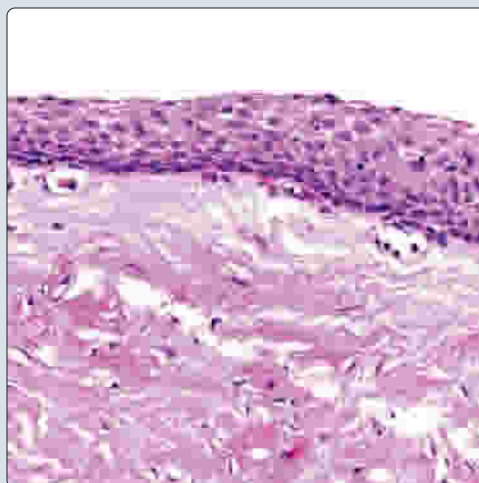


Gross of Dentigerous Cyst

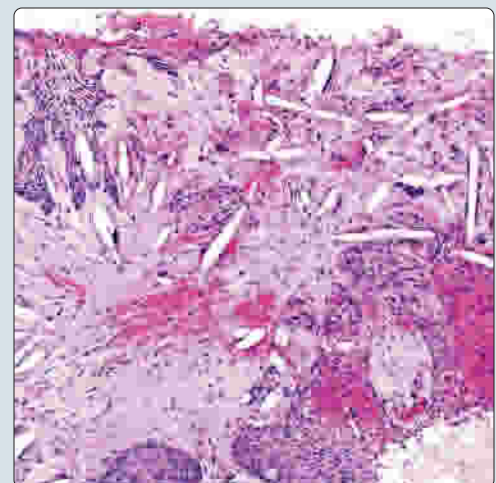


Thin Epithelial Lining

(Left) There is a thin (8-10 cell layers thick) squamous epithelium lining the cystic space. There is fibrous connective tissue stroma. There is no palisading, no nuclear polarization, no subnuclear vacuolization, and no parakeratinizing layer, helping to exclude items in the differential diagnosis. (Right) There are numerous cholesterol clefts with blood in this area of reaction within a dentigerous cyst. The epithelium is much thicker and shows hyperplasia when there are reactive changes.



Cholesterol Clefts in Dentigerous Cyst



TERMINOLOGY

Definitions

- Developmental cyst surrounding crown of impacted tooth and attached to cemento-enamel junction

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Develops by accumulation of fluid between reduced enamel epithelium and crown of tooth

CLINICAL ISSUES

Epidemiology

- Incidence
 - Most common developmental cyst
 - 25% of all jaw cysts
- Age
 - Wide range (5-83 years)
 - Peak incidence: 2nd-3rd decades (mean: 33 years)
- Sex
 - Male predilection: Male > female (1.7:1)

Site

- Mandible > maxilla (1.8:1)
- Most commonly associated with mandibular 3rd molars
- Then, maxillary canines, maxillary 3rd molars, mandibular 2nd premolars

Presentation

- Small cyst may be asymptomatic
 - Discovered on routine dental radiographs
- Expansion of bone with pain
- Resorption of adjacent teeth
- Associated with supernumerary teeth (~10%)
- Infection is usually associated with oral communication

Treatment

- Careful enucleation of cyst
- Extraction
- Preservation of tooth may be indicated
- Large cysts are occasionally treated with marsupialization

Prognosis

- Excellent, with rare recurrence
- Rare cases of malignant transformation

IMAGING

Radiographic Findings

- Usually unilocular radiolucency around crown of affected tooth
- Well-defined sclerotic border
- Larger lesions may appear multilocular
- May displace involved tooth
- Mandibular 3rd molars
- Maxillary canines
- Relationship to tooth
 - **Central:** Surrounds crown of tooth
 - **Lateral:** Cyst grows laterally along root and partially surrounds crown
 - **Circumferential:** Surrounds crown and much of root

MACROSCOPIC

General Features

- Fibrous tan friable soft tissue
- Extracted tooth

MICROSCOPIC

Histologic Features

- Noninflamed
 - Fibrous to fibromyxoid connective tissue
 - 2-3 layers of cuboidal to ovoid squamoid epithelium
 - Occasional mucous cells
 - Rare ciliated cells
 - Rare sebaceous cells
 - Occasional dystrophic calcifications in stroma
- Inflamed
 - Fibrous connective tissue
 - Proliferative epithelium
 - Hyperplastic rete ridges
 - Chronic inflammatory cells
 - Acute inflammatory cells, usually associated with oral communication
 - Cholesterol clefts (common)
- Odontogenic epithelial rests (~20%)
- Rushton bodies

ANCILLARY TESTS

Genetic Testing

- *PTCH1* is inactivated

DIFFERENTIAL DIAGNOSIS

Enlarged Dental Follicle

- Usually < 3-4 mm radiographically
- No cystic epithelium

Glandular Odontogenic Cyst

- Generally, anterior mandible, with cortical perforation, developing in 5th decade, with high recurrence risk
- Squamous epithelium with flat interface to adjacent tissue, plaque-like thickenings with whorled epithelium, cuboidal eosinophilic hobnail cells, mucus or goblet cells, and duct-like structures

Unicystic Ameloblastoma

- Thin epithelium, with ameloblastic changes, and umbrella cells with stellate reticulum

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KEY FACTS

TERMINOLOGY

- Glandular odontogenic cyst (GOC)
- Benign developmental odontogenic cyst showing glandular differentiation

CLINICAL ISSUES

- Mean: 5th-7th decades
- Equal gender distribution, although some areas show male predilection
- 80% occurred in mandible
- 60% involve anterior jaws
- Swelling or expansion (buccolingual)
- Enucleation, curettage, cystectomy, excision
- Significant recurrence rate (20-50%)

IMAGING

- Well-defined unilocular (most common) or multilocular radiolucency, sometimes with scalloped border

MICROSCOPIC

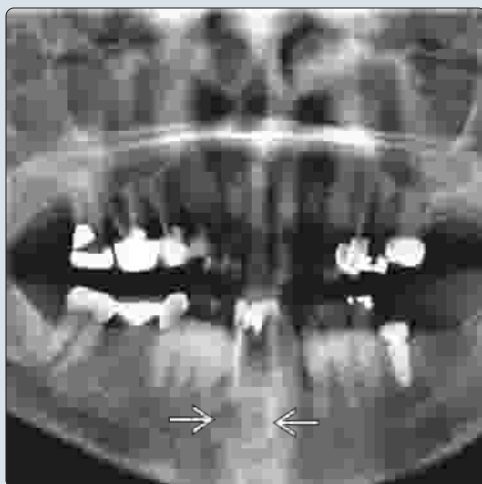
- Eosinophilic, hobnail cells
- Microcysts
- Apocrine snouting
- Clear or vacuolated cells
- Variable thickness of epithelial cyst lining
- Papillary projections (tufting)
- Mucous goblet cells
- Epithelial spheres
- Cilia
- Multiple compartments

TOP DIFFERENTIAL DIAGNOSES

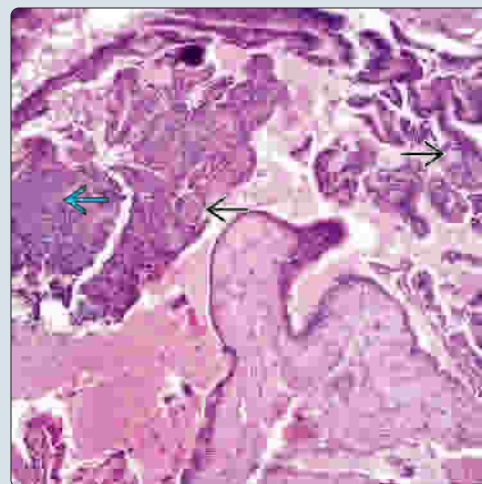
- Central mucoepidermoid carcinoma
- Dentigerous cyst
- Botryoid odontogenic cyst

Radiograph of Glandular Odontogenic Cyst

(Left) There is a well-defined, radiolucent mass involving the anterior mandible. Note the slightly sclerotic border. The teeth roots are focally splayed. (Courtesy B. L. Nelson, DDS.) (Right) Multiple papillary projections are noted. There are many microcysts. Plaque-like thickenings, similar to a lateral periodontal cyst, create epithelial spheres. Mucocytes and squamous epithelium are easily identified throughout.



Complex Glandular Proliferation

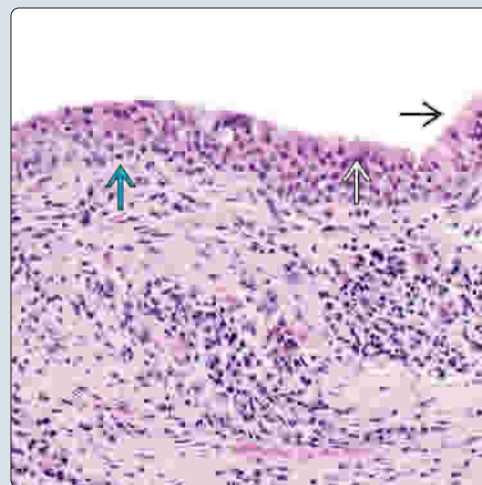


Mucinous Differentiation

(Left) Mucinous cells are easily identified throughout this proliferation. Ciliated surface epithelium is present. (Right) While mucocytes are easily identified, the more subtle clear cells, hobnail cells, and ciliated cells require additional careful evaluation. Not all of the features of glandular odontogenic cyst (GOC) are seen in the same field, requiring many sections and even levels to detect the histologic findings.



Mucocytes, Ciliated and Clear Cells



TERMINOLOGY

Abbreviations

- Glandular odontogenic cyst (GOC)

Definitions

- Benign developmental odontogenic cyst showing glandular differentiation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare: 0.2% of all odontogenic cysts
- Age
 - Mean: 5th-7th decades
 - Range: 20-86 years
- Sex
 - Equal gender distribution, although some areas show male predilection

Site

- 80% occurred in mandible
- 20% in maxilla; usually involves canine area
- 60% involve anterior jaws

Presentation

- Swelling or expansion (buccolingual)
- Many are asymptomatic
- Pain, discomfort, or infection are uncommon

Treatment

- Surgical approaches
 - Conservative: Enucleation, curettage, excision

Prognosis

- Significant recurrence rate (20-50%)
 - 1st recurrence is 5-8 years after initial treatment
- Multiple recurrences are common

IMAGING

Radiographic Findings

- Well-defined unilocular (most common) or multilocular radiolucency, sometimes with scalloped border
- Periapical area of multiple teeth, often with root resorption
- Association with unerupted tooth may be seen (~ 20%)
- Cortical perforation and teeth displacement are uncommon

MICROSCOPIC

Histologic Features

- Eosinophilic, hobnail cells
 - Surface cyst lining cells resembling cuboidal cells of reduced enamel epithelium
- Microcysts
 - Duct-like spaces lined by single layer of cuboidal to columnar cells
 - May be lined by mucous goblet cells
 - Mucous pools, eosinophilic material, or may be empty
- Apocrine snouting

- Decapitation secretions or pinching off of surface epithelium
- Clear or vacuolated cells
 - Clear cytoplasm seen in basal or parabasal areas
 - If epithelium is thin, may be adjacent to surface cells
- Variable thickness of epithelial cyst lining
 - Must be significant variability in thickness from one area to next
- Papillary projections (tufting)
 - Sometimes several microcysts opening onto surface will create them
- Mucous goblet cells
 - Single or clustered on surface or within microcysts
- Epithelial spheres
 - Plaque-like thickenings, similar to lateral periodontal cyst
- Cilia
 - True cilia, different from apocrine snouting
- Multiple compartments
 - Multiple cystic spaces similar to botryoid odontogenic cysts

DIFFERENTIAL DIAGNOSIS

Central Mucoepidermoid Carcinoma

- Transitional epithelium, cytologic atypia, invasion, and increased mitoses
- *MECT1:MAML2* fusion is positive in low-grade tumors (absent in GOC)

Dentigerous Cyst

- Dentigerous cyst with metaplastic changes, shows prominent intercellular bridges
- Lacks microcysts, clear cells, and epithelial spheres

Botryoid Odontogenic Cyst

- Similar to lateral periodontal cyst, but loculated
- Thin lining of nonkeratinized epithelium with focal thickenings

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Most significant features: Microcysts, epithelial spheres, clear cells, variable thickness, and multiple compartments

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KEY FACTS

TERMINOLOGY

- Benign simple odontogenic cyst lined by ameloblastoma-like epithelium with ghost cells that may calcify
- Gorlin cyst

CLINICAL ISSUES

- Wide age range (mean: 30 years), equal gender distribution
- Maxilla favored slightly, usually anterior
- May be associated with other odontogenic tumors
- Bone radiolucency, often with unerupted tooth
- **Central (intraosseous)**
 - Maxilla slightly more often: Anterior most frequently
- **Peripheral (gingiva/alveolar mucosa)**
 - Gingiva and alveolar mucosa
- Excellent prognosis; few recurrences documented

IMAGING

- **Central**
 - Unilocular or multilocular

- Radiolucent with well-defined margin
- Contains irregular internal calcifications, especially at periphery

• Peripheral

- May show soft tissue calcification and cupping

MICROSCOPIC

- Classified as central and peripheral
- Thin epithelium with columnar or cuboidal basal cells (ameloblast-like)
- Ghost cells: Most characteristic finding
- Calcified material

TOP DIFFERENTIAL DIAGNOSES

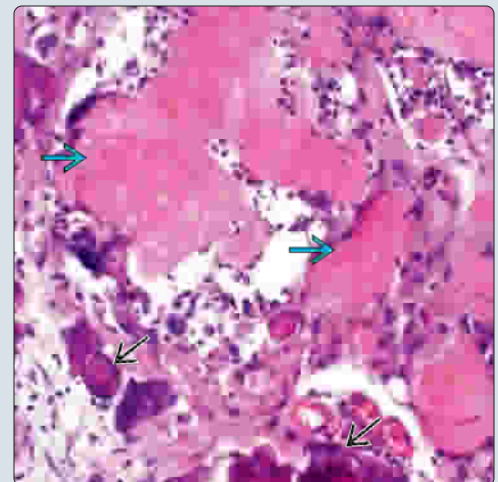
- Ameloblastoma
- Odontogenic cysts, peripheral ossifying fibroma
- Craniopharyngioma
- Squamous cell carcinoma, *NUT1* midline carcinoma

Peripheral CCOT With Ghost Cells



(Left) Peripheral variants of CCOT are not uncommon, making up approximately 1/3 of all tumors. In this image, epithelium from the overlying gingiva can be seen adjacent to neoplastic ghost cells. This variant has a more solid appearance clinically. (Right) High-power image shows the characteristic ghost cells, large epithelial cells with loss of nuclei. These areas are blended with areas of calcified material.

Ghost Cells Mixed With Calcified Areas

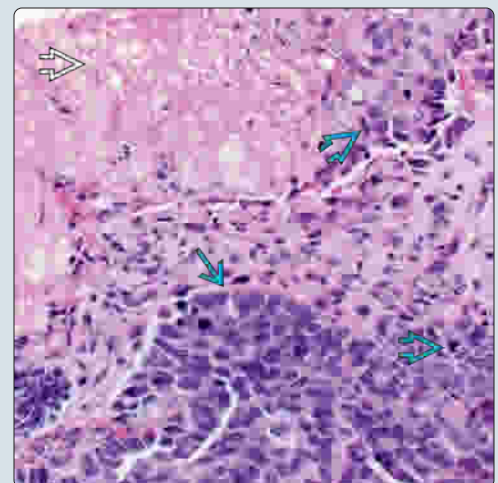


Cystic Epithelium With Ghost Cells



(Left) A primarily unicystic tumor with focal daughter cysts is shown. The epithelium, even at this moderate power, has an ameloblastic look, with the lumen lined by epithelium that resembles stellate reticulum. Ghost cells are easily identified. (Right) This malignant variant of the calcifying cystic odontogenic tumor is from the maxilla of a middle-aged woman. Note the hyperchromatic and pleomorphic epithelial cells. Mitoses and ghost cells are easily identified.

Ghost Cell Odontogenic Carcinoma



TERMINOLOGY

Abbreviations

- Calcifying odontogenic cyst (COC); calcifying cystic odontogenic tumor (CCOT); calcifying ghost cell odontogenic cyst (CGCOC); ghost cell odontogenic carcinoma (GCOC)

Synonyms

- Gorlin cyst (1st described by Gorlin in 1962)
- Calcifying odontogenic cyst
- Part of ghost cell odontogenic tumors (solid variants are rare)

Definitions

- Benign simple odontogenic cyst lined by ameloblastoma-like epithelium with ghost cells that may calcify
 - Separated into **central** (intraosseous) and **peripheral** (gingiva/alveolar mucosa)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon, < 1% of all odontogenic cysts
- Age
 - Wide range: 2nd and 3rd decades most common
 - If associated with odontoma: Younger age group
 - Aggressive variants/carcinoma: More common in older patients
- Sex
 - Equal gender distribution

Site

- **Central (intraosseous)**
 - Maxilla slightly more often (anterior most frequently); anterior mandible
- **Peripheral (gingiva/alveolar mucosa)**
 - Gingiva and alveolar mucosa; up to 1/3 of tumors
 - Usually anterior to 1st molar: Incisor-canine area

Presentation

- Pain, bony expansion
- Asymptomatic, incidental finding on routine radiographs
- May be associated with other odontogenic tumors
- Peripheral lesions appear as nondescript gingival masses
- Multiple, synchronous tumors may be seen

Treatment

- Calcifying odontogenic cyst: Simple enucleation
- Calcifying odontogenic cyst with other odontogenic tumor(s): Treat for the more aggressive lesion
- Peripheral cysts: Simple excision

Prognosis

- Excellent prognosis; few recurrences documented
- If associated with another tumor, prognosis reflects more aggressive tumor
- GCOC: Unpredictable, but generally considered to have poor prognosis

IMAGING

Radiographic Findings

- **Central**
 - Unilocular or multilocular
 - Radiolucent with well-defined margin
 - Contains irregular internal calcifications, especially at periphery
 - May be associated with unerupted/impacted tooth
 - Root resorption and root divergence may be seen
- **Peripheral**
 - May show soft tissue calcification and cupping

MICROSCOPIC

Histologic Features

- Cysts may be nonproliferative (simple), proliferative, ameloblastomas, combined with odontoma, or combined with other odontogenic tumors
- **Cysts**
 - May be unicystic (most common) or multicystic with daughter cysts
 - Thin epithelium with columnar or cuboidal basal cells (ameloblast-like) along fibrous wall
 - Lumen lined by tissue resembling stellate reticulum
- **Ghost cells**
 - Most characteristic finding (few entities have them)
 - Large epithelial cells with loss of nuclei
 - Develop as a result of coagulative necrosis
- **Calcified material**
 - May be associated with other odontogenic tumors
 - Most common is odontoma (compound)
 - Ameloblastoma, ghost cell odontogenic carcinoma
- GCOC: Pleomorphism, increased mitoses

DIFFERENTIAL DIAGNOSIS

Ameloblastoma

- No ghost cells

Peripheral Ossifying Fibroma

- Gingival mass with bone, lacking ghost cells

Craniopharyngioma

- Histologically identical, affects children, but with pituitary/sellar involvement

Squamous Cell Carcinoma

- Differential for GCOC; tend not to have ghost cells; *NUT1* midline carcinoma has abrupt keratinization

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KEY FACTS

TERMINOLOGY

- Nonkeratinized and noninflammatory developmental cyst located adjacent or lateral to root of vital tooth

ETIOLOGY/PATHOGENESIS

- Debate about derivation from dental lamina, reduced enamel epithelium, primordial cyst, or rests of Malassez

CLINICAL ISSUES

- Age range: 14-85 years (mean: 5th-7th decades)
- Men and women equally affected
- Majority affect mandible (up to 75%), lateral incisor to premolar
- Asymptomatic, incidental discovery on routine dental imaging
- Preserved vitality of adjacent erupted teeth (unless tooth is absent)
- Conservative enucleation is treatment of choice

IMAGING

- Well-delineated, well-corticated, radiolucent, unicystic; round, teardrop, or oval cyst between teeth (interradicular)

MICROSCOPIC

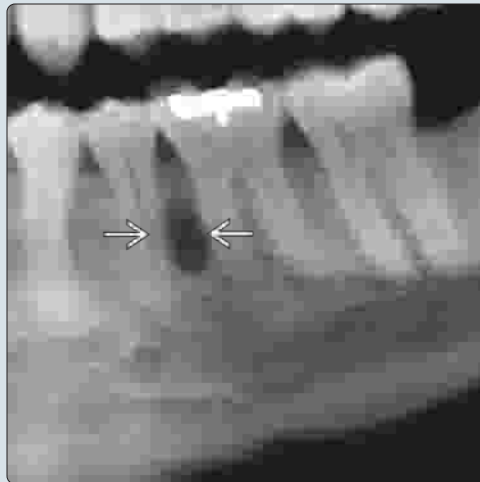
- Cystic cavity lined by thin, stratified, nonkeratinizing squamous epithelium, 1-5 cell layers thick
 - Glycogen-rich, clear cells interspersed within epithelium in many cases
- Focal plaque-like to nodular epithelial thickenings within wall
 - Whorled, swirled in appearance, continuous with epithelium
- Thick fibrous connective tissue wall, usually with limited inflammation

TOP DIFFERENTIAL DIAGNOSES

- Gingival cyst, glandular odontogenic cyst, keratocystic odontogenic tumor, unicystic ameloblastoma

Panorex of Lateral Periodontal Cyst

(Left) There is a well-defined, oval radiolucency ➡ identified between tooth 19 and 20. Both of the teeth are vital, although tooth 19 has a restoration. (Right) This CT image shows a well-defined and well-delimited radiolucent cyst ➡ adjacent to the tooth root and noted in an interradicular position.

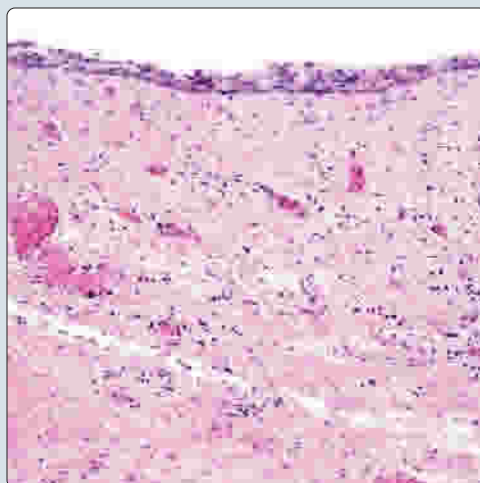


Well-Defined Radiolucent Cyst

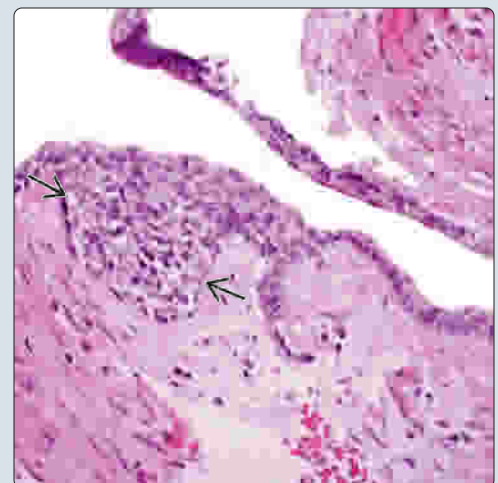


Thin, Nonkeratinizing Epithelium

(Left) There is a 3-4 cell layer thick squamous nonkeratinizing epithelium lining this cyst. There is a thick fibrous connective tissue stroma below. These findings can be nonspecific without the imaging correlation. (Right) The thin squamous epithelium shows a plaque ➡ of slightly whorled epithelium that has pushed into the stroma below. These plaques are quite helpful in the diagnosis.



Plaque Within Cyst Wall



TERMINOLOGY

Abbreviations

- Lateral periodontal cyst (LPC)

Synonyms

- Botryoid odontogenic cyst (BOC) is multicystic variant

Definitions

- Nonkeratinized and noninflammatory developmental cyst located adjacent or lateral to root of vital tooth
 - Unicystic or multicystic (BOC)
- LPC and gingival cyst of adult (GCA) represent intraosseous and extraosseous manifestations, respectively, of same lesion

ETIOLOGY/PATHOGENESIS

Developmental

- Debate about derivation from dental lamina, reduced enamel epithelium, primordial cyst or rests of Malassez

CLINICAL ISSUES

Epidemiology

- Incidence
 - < 1% of odontogenic cysts
- Age
 - Range: 14-85 years (mean: 5th-7th decades)
 - Females affected at younger age than males
- Sex
 - Men and women equally affected
- Ethnicity
 - Whites > blacks

Site

- Majority affect mandible (up to 75%), lateral incisor to premolar
- Less commonly in anterior maxilla

Presentation

- Asymptomatic, incidental discovery on dental imaging
- Preserved vitality of adjacent erupted teeth

Treatment

- Conservative enucleation is treatment of choice

Prognosis

- Excellent, with only rare recurrences reported (usually BOC)

IMAGING

Radiographic Findings

- Well-delineated, well-corticated, radiolucent, unicystic; round, teardrop, or oval cyst between teeth (interradicular)
- BOC: Presents as multilocular radiolucency (cluster of grapes)

MACROSCOPIC

General Features

- Thin-walled, soft-tissue sac with nodular excrescences

Size

- Usually < 1 cm

MICROSCOPIC

Histologic Features

- Cystic cavity lined by thin, stratified, nonkeratinizing squamous epithelium, 1-5 cell layers thick
 - Glycogen-rich, clear cells interspersed within epithelium in many cases
 - Clear cells of dental lamina rests are nearly identical to those lining LPC
- Thick connective tissue wall with limited inflammation
 - Hyalinized areas subjacent to cystic epithelium
- Focal plaque-like to nodular epithelial thickenings
 - Whorled or swirled, continuous with epithelium
 - May expand into the fibrous connective tissue or protrude into lumen
- Absent stromal-epithelial clefting, basal palisade, reverse polarization, and parakeratinized layer
- BOC: More pronounced plaque-like thickenings, mural protrusions, multilocular appearance
- Melanin pigment within cyst lining is rare

DIFFERENTIAL DIAGNOSIS

Gingival Cyst

- Gingival cyst when there is gingival attachment

Glandular Odontogenic Cyst

- Variable thick epithelium, eosinophilic, hobnail cells lining microcysts, with mucocytes, apocrine snouts, and clear cells

Keratocystic Odontogenic Tumor

- Thin keratinizing squamous lining, refractile, parakeratinized layer, basal palisade of columnar cells, with stromal separation

Unicystic Ameloblastoma

- Reverse polarization, "umbrella" cells lining cavity, separation from stroma, and no inflammation

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KEY FACTS

TERMINOLOGY

- Inflamed tissue associated with apex or root surface of nonvital tooth
- Arc of development: Epithelial lined cyst undergoes intense inflammation, with eventually involution of epithelium, leaving residual inflammation and fibrosis

CLINICAL ISSUES

- Caries causes cavitation of tooth, which leads to bacterial invasion of pulp tissue, releasing toxins, and pulp tissue is devitalized
- Periapical cyst is most common jaw cyst
- Asymptomatic or symptomatic
- Always associated with root surface of tooth
- Endodontic treatment, extraction, or antibiotic therapy

IMAGING

- Radiolucency associated with apex or root surface
- Variable size, circumscribed to poorly circumscribed

MICROSCOPIC

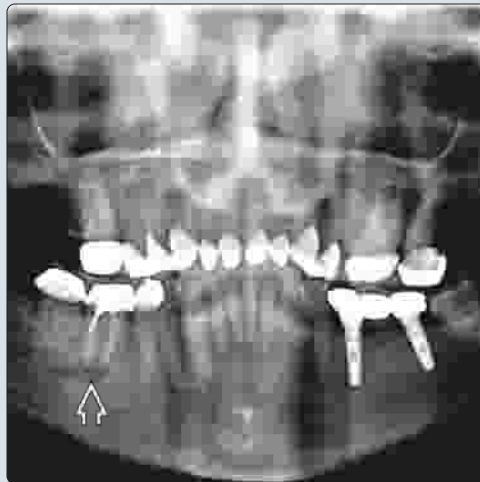
- Periapical cyst with stratified squamous epithelium
- Chronic and acute: Lymphocytes, plasma cells, multinucleated giant cells, histocytes, eosinophils, and neutrophils
- Dystrophic calcifications
- Fibrous tissue
- Cholesterol clefts

TOP DIFFERENTIAL DIAGNOSES

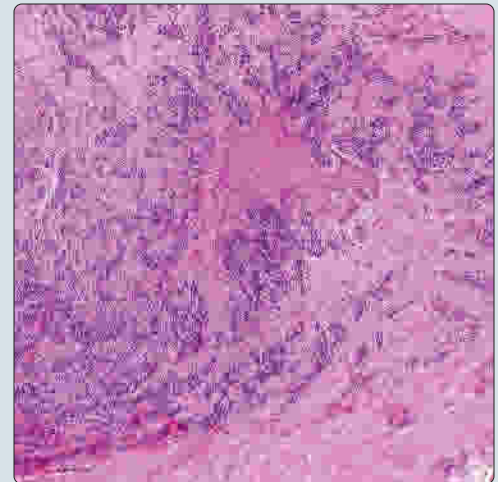
- Scar
- Keratinizing odontogenic tumor (odontogenic keratocyst)
- Orthokeratinized odontogenic cyst
- Lateral periodontal cyst
- Nasopalatine duct cyst

Panorex of Periapical Cyst

(Left) This orthopantomograph (Panorex) shows significant dental work. However, there is a nonvital tooth [X] that is associated with a poorly defined radiolucency at the apex of the root, which was a periapical cyst. (Right) There is a very rich inflammatory infiltrate associated with a hyperplastic squamous epithelium. This is nonspecific, requiring correlation with the imaging and clinical findings.



Periapical Cyst and Granuloma

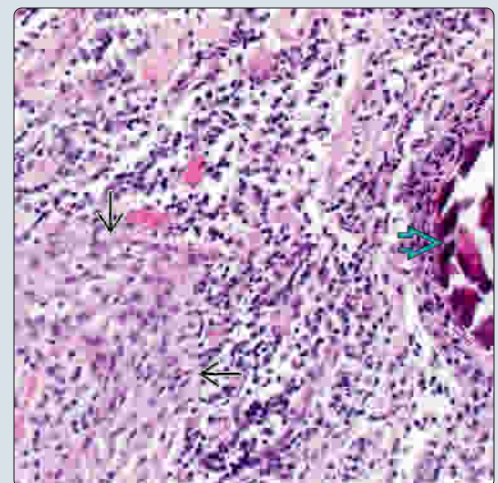


Inflammation and Calcification

(Left) There are sheets of inflammatory cells with heavy stromal fibrosis and isolated calcifications [X]. These findings are nonspecific, but are diagnostic of a periapical granuloma in the correct imaging setting. (Right) There is a limited amount of epithelium [X] in this inflamed stroma associated with dystrophic calcifications [X]. These changes are part of a periapical cyst.



Epithelium in Periapical Cyst



TERMINOLOGY

Synonyms

- Periapical cyst
- Periapical granuloma

Definitions

- Inflamed tissue associated with apex or root surface of nonvital tooth
- Arc of development: Epithelial lined cyst undergoes intense inflammation, with eventually involution of epithelium, leaving residual inflammation and fibrosis

CLINICAL ISSUES

Epidemiology

- Incidence
 - Periapical cyst
 - Most common jaw cyst
 - ~ 75% periapical lesions
 - Periapical granuloma
 - Less common
- Age
 - Wide range
- Sex
 - Equal gender distribution

Site

- Always associated with root surface of tooth

Presentation

- Asymptomatic
 - May be detected during routine dental radiographs
- Symptomatic
 - Pain
 - Sensitivity to temperature changes
 - Mobility of affected teeth

Natural History

- Caries causes cavitation of tooth, which leads to bacterial invasion of pulp tissue, releasing toxins, and pulp tissue is devitalized

Treatment

- Endodontic treatment
 - Nonsurgical endodontic therapy (root canal)
 - Surgical endodontic therapy for nonsurgical failures or large lesions
- Extraction of associated tooth or teeth
- Antibiotic treatment for lesions with acute infections, especially actinomycosis

Prognosis

- Good with appropriate treatment

IMAGING

Radiographic Findings

- Radiolucency
 - Variable size, circumscribed to poorly circumscribed
 - Associated with apex or root surface
 - May cause root resorption
- Associated tooth conditions

- Caries or fracture, large restoration, previous endodontic therapy

MACROSCOPIC

General Features

- Attached apical tissue on extracted tooth

MICROSCOPIC

Histologic Features

- Fibrous tissue
- Periapical cyst
 - Stratified squamous epithelial lining
- Inflammation is variable
 - Chronic and acute: Lymphocytes, plasma cells, multinucleated giant cells, histiocytes, eosinophils, and neutrophils
- Dystrophic calcifications
- Cholesterol clefts
- Foreign material if previously endodontically treated

DIFFERENTIAL DIAGNOSIS

Scar

- Dense fibrous connective tissue with little inflammation

Keratinizing Odontogenic Tumor (Odontogenic Keratocyst)

- Usually lacks inflammation
- Epithelial surface
 - Lack of rete ridges
 - Parakeratotic with corrugated appearance
 - 6-8 cells thick with palisaded, hyperchromatic basal layer

Orthokeratinized Odontogenic Cyst

- Usually lacks inflammation
- Orthokeratinized epithelial surface

Lateral Periodontal Cyst

- Usually lacks inflammation
- Thin epithelial lining with focal thickenings

Nasopalatine Duct Cyst

- Limited to anterior palate
- Variety of epithelial types
- Associated with blood vessels, nerves, and occasionally minor salivary glands

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KEY FACTS

TERMINOLOGY

- Odontogenic cyst characterized by thin regular lining of parakeratinised stratified squamous epithelium with palisaded, hyperchromatic basal cells

ETIOLOGY/PATHOGENESIS

- Arise from cells of dental lamina
- Nevoid basal cell carcinoma syndrome (Gorlin syndrome) is associated with multiple odontogenic keratocysts

CLINICAL ISSUES

- Predilection for mandible
- Peak in 2nd-3rd decades and 2nd smaller peak in 50-70-year age group
- Multiple recurrences
- Nevoid basal cell carcinoma syndrome (~ 5%)
 - Basal cell carcinomas, skeletal anomalies, medulloblastoma; ovarian and cardiac fibromas

IMAGING

- Well-defined, unilocular radiolucency, with smooth corticated border

MACROSCOPIC

- Thin, friable soft tissue with keratinaceous debris

MICROSCOPIC

- Thin epithelial lining, with retraction artifacts
- 6-8 cells thick without rete ridges
- Parakeratotic surface layer, with wavy, corrugated surface
- Basal layer shows palisading and hyperchromicity
- Inflammation may alter characteristic histology

ANCILLARY TESTS

- High Ki-67 labeling and overexpressed *TP53*

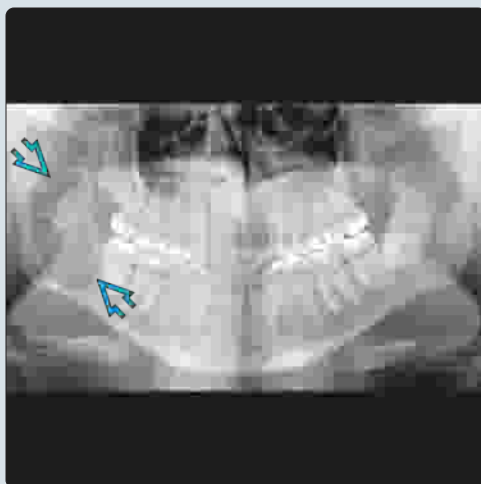
TOP DIFFERENTIAL DIAGNOSES

- Orthokeratinized odontogenic cyst; dentigerous cyst

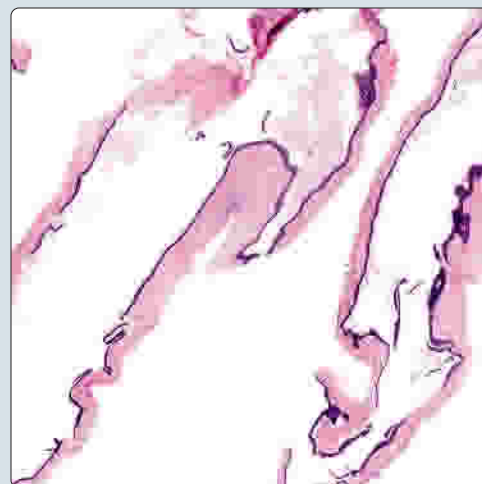
Large Radiolucent Mandibular Cyst

(Left) Orthopantomograph (Panorex) shows a large, lytic mass within the right mandible. There is a smooth, sclerotic border, but no teeth are noted within the cyst.

(Right) Odontogenic keratocysts (OKCs) generally have thin friable walls and a distinctive lumen. Even at this magnification, rete are not visible, and there is a very thin epithelial lining of the cystic cavity. Limited keratin is noted.

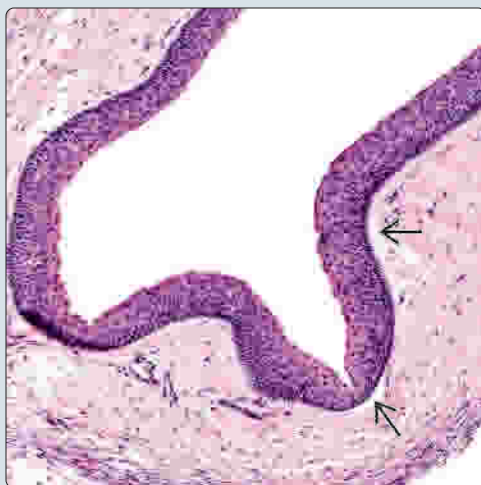


Strips of Epithelium With Fibrosis



Retraction of Epithelium

(Left) This cyst is lined by a relatively thin epithelium, showing a flat interface with the fibrous connective tissue. A cleft (retraction) is often present, an artifact of processing resulting from the lack of well-developed rete ridges. (Right) Cells of the basal layer of the epithelium show characteristic palisading and hyperchromicity. There is no reverse polarization. The epithelium is 6-8 cells thick and demonstrates a wavy, parakeratinized surface.



Parakeratinized Layer and Nuclear Palisading



TERMINOLOGY

Abbreviations

- Odontogenic keratocyst (OKC)

Synonyms

- Keratocystic odontogenic tumor

Definitions

- Odontogenic cyst characterized by thin regular lining of parakeratinized stratified squamous epithelium with palisaded, hyperchromatic basal cells

ETIOLOGY/PATHOGENESIS

Histogenesis

- May arise from cells of dental lamina

Inherited Condition

- Nevoid basal cell carcinoma syndrome (NBCCS), Gorlin syndrome, Gorlin-Goltz syndrome
 - Autosomal dominant trait, with high penetrance, variable expression; often spontaneous mutations

CLINICAL ISSUES

Epidemiology

- Incidence
 - 10-20% of odontogenic cysts
- Age
 - Wide range, peak in 2nd-3rd decades and 2nd smaller peak in 50-70-year age group
 - Cysts found at earlier age in those with NBCCS
- Sex
 - Male > female (2:1)
- Ethnicity
 - Whites affected most commonly

Site

- Predilection for mandible (80%) (3x > maxilla)
 - Posterior and ascending ramus
- Maxillary lesions tend to be smaller

Presentation

- Asymptomatic (~ 1/3)
- Swelling, pain, facial asymmetry, and discomfort
 - Tends to grow in anteroposterior direction, failing to alter lateral bone walls
- Rarely, intraoral drainage and neurologic symptoms due to nerve compression
- NBCCS (~ 5% of OKC patients)
 - Multiple OKCs are consistent feature in ~ 75% of patients
 - Basal cell carcinomas at a young age, typically in non-sun-exposed areas
 - Skeletal anomalies

Treatment

- Surgical approaches
 - Enucleation or curettage ± osteotomy

Prognosis

- Multiple recurrences (~ 25% of cases), more common in NBCCS

IMAGING

Radiographic Findings

- Well-defined, smooth, corticated border, uni-/multilocular radiolucency
- Associated with unerupted, displaced teeth (up to 40%)

MICROSCOPIC

Histologic Features

- Epithelial lining
 - 6-8 cells thick
 - Lacks rete ridges, creates clefts (retraction) artifacts between fibrous wall and epithelium
 - Basal layer shows palisading and hyperchromatic nuclei
 - Parakeratotic epithelial cells at surface
 - Wavy or corrugated surface keratinization (refractile)
 - Keratinaceous debris in lumen
- Fibrous connective tissue
 - Often detached from overlying epithelium
- When inflamed, epithelium is altered
 - Acute and chronic inflammatory cells
 - Characteristic histology altered, with rete noted
- Epithelial hyaline bodies (Rushton bodies)
 - Refractile, brightly eosinophilic curvilinear bodies in keratin
- Nevoid basal cell carcinoma syndrome
 - More satellite cysts, daughter cysts, budding, and proliferative odontogenic epithelial rests
- Rarely, malignant transformation

ANCILLARY TESTS

Immunohistochemistry

- High Ki-67 labeling confirms proliferation
- *TP53* overexpressed

Genetic Testing

- *PTCH1* gene (chromosome 9q22.3-q31) is tumor suppressor gene, which shows loss of function in OKC
 - Results in overexpression of *BCL2* and *TP53*

DIFFERENTIAL DIAGNOSIS

Orthokeratinized Odontogenic Cyst

- Orthokeratotic epithelial lumen surface, prominent keratohyaline granules, no basal palisade

Dentigerous Cyst

- Unerupted tooth; thin, nonkeratinized epithelium

Periapical Cyst

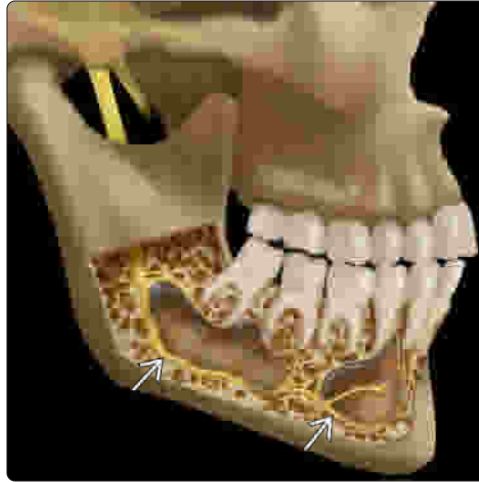
- Radicular surface of nonvital tooth, stratified squamous epithelium with dense inflammation

SELECTED REFERENCES

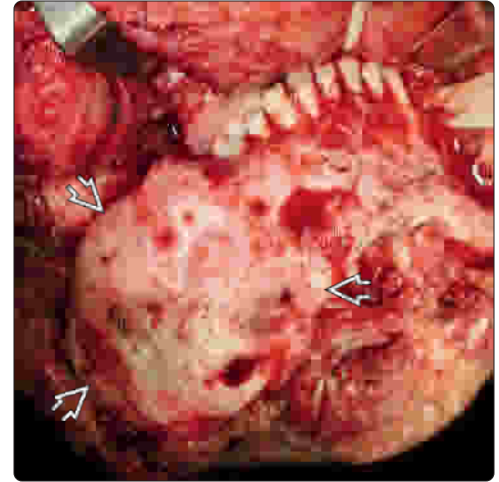
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Multiple Cysts: Syndrome-Associated OKC

(Left) Lateral graphic with outer mandibular cortex removed shows the classic appearance of multiple OKCs in nevoid basal cell carcinoma syndrome (NBCCS). Lesions splay teeth roots and displace the inferior alveolar nerve. Tooth resorption is not a common finding. (Right) The mandible of this patient contains a large protuberant mass expanding the borders of the bone. Excision of this size lesion may result in cosmetic deformity.



Gross of Large Mandibular Mass

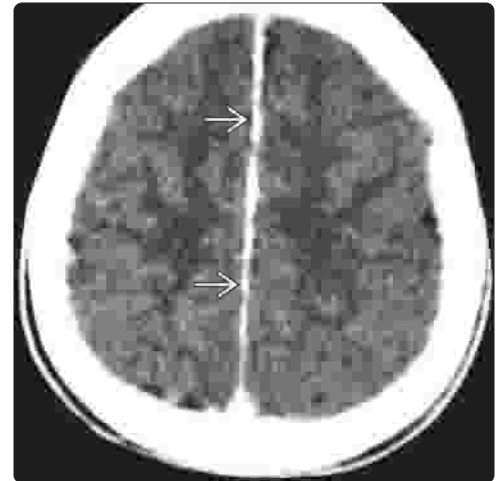


CT of Radiolucent Cyst With Tooth

(Left) There is expansion of this mass in the maxillary sinus. Note the intact tooth within the cavity, which is otherwise filled with radiopaque material, which may be secretions or degenerated material. (Right) Axial NECT shows calcified falx cerebri in a child with NBCCS. Skeletal abnormalities are a common finding in those affected by the syndrome and include bifid ribs and kyphoscoliosis.



Calcified Falx Cerebri

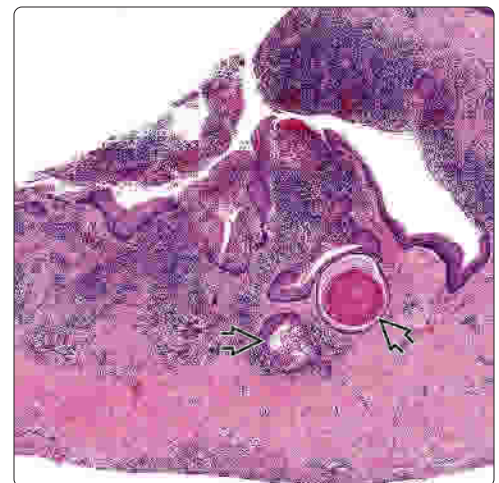


Plantar Pits

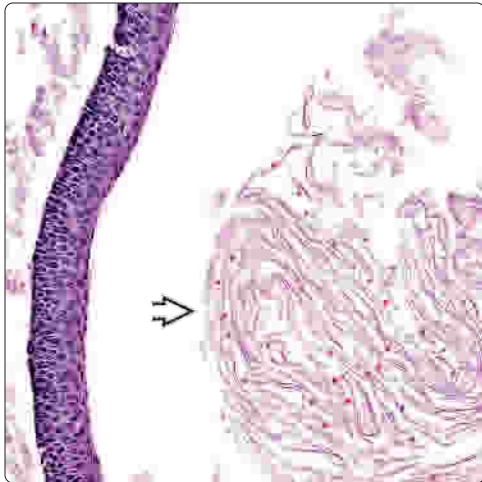
(Left) Plantar and palmar pits are a common finding in NBCCS. These pits are a result of the alteration in the development of the basal epithelial cells. (Right) Daughter or satellite cysts are more frequently seen in patients with Gorlin syndrome or NBCCS. This lesion is also notable for the dense inflammatory infiltrate within the fibrous stroma.



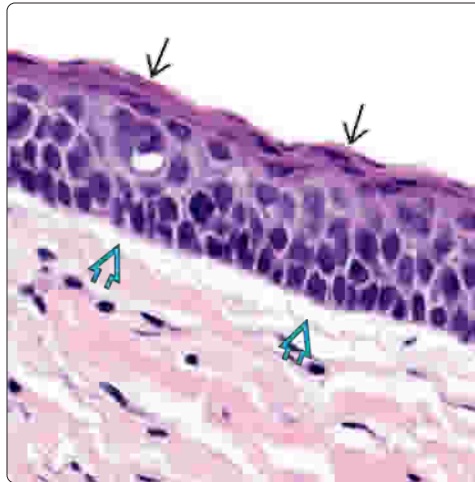
Satellite Cysts: Syndrome-Associated OKC



Detached Epithelium With Keratin

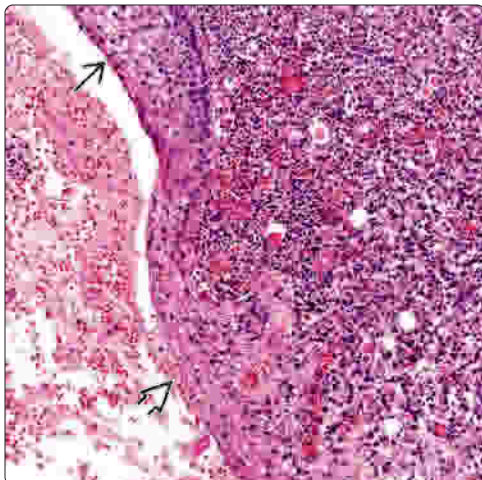


Marked Retraction Artifact and Parakeratinized Surface

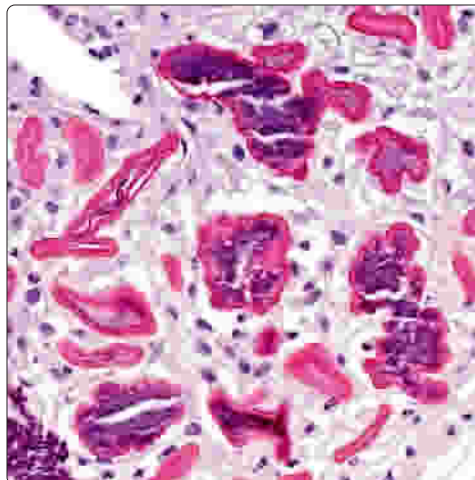


(Left) A thin portion of epithelium is detached from the underlying fibrovascular connective tissue, a common finding in this lesion because of the lack of rete ridges. Keratinaceous debris is noted in the lumen. (Right) A thin portion of epithelium has become detached (retraction artifact) from the underlying fibrovascular connective tissue, a common finding in this lesion because of the lack of rete ridges. Note the bright parakeratinized layer.

Inflamed OKC

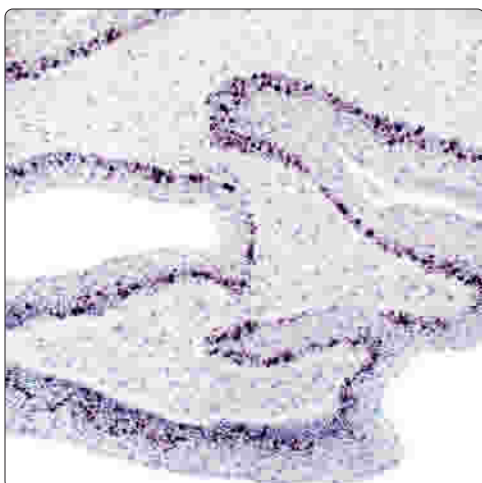


Rushton Bodies

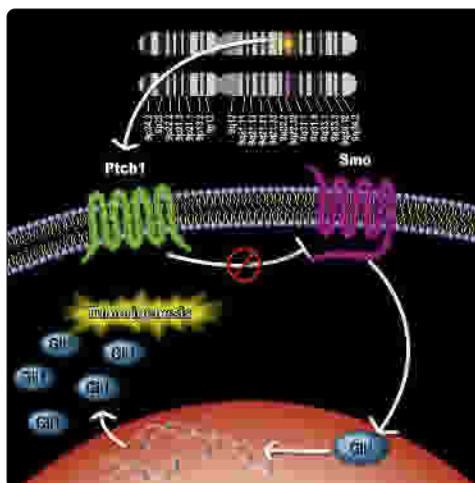


(Left) Note the transition of the epithelium from the characteristic, well-organized, noninflamed area into an area of dense inflammation. When inflamed, the native cyst type is more difficult to determine. (Right) Rushton bodies are not pathognomonic of OKC but are a useful finding. They represent a breakdown product (of keratin) combined with debris, calcified material, and products of blood. This refractile material is most commonly identified in areas of inflammation.

Increased Ki-67 Labeling



PTCH1 Mutation



(Left) There is a greatly increased number of Ki-67 labeled cells, highlighting the proliferative nature of this tumor. p53 also shows an increased expression in OKC (not shown). (Right) As shown in this graphic representation, PTCH1 mutation activates downstream targets, including SMO, which results in GLI1 and consequent tumorigenesis.

KEY FACTS

TERMINOLOGY

- Locally aggressive, benign, epithelial odontogenic neoplasm arising from remnants of odontogenic epithelium

CLINICAL ISSUES

- Most common odontogenic tumor, excluding odontomas
- 80-85% occur in posterior mandible; peripheral variant found on gingiva
- Usually asymptomatic
 - Oftentimes incidental findings on routine dental radiographs
- Painless swelling, expansion of jaw

IMAGING

- Conventional types usually appear as multilocular radiolucencies

MICROSCOPIC

- Blend of ameloblasts and epithelial cells trying to reduplicate enamel organ
- Ameloblastic cells are palisaded about periphery of tumor nests in jigsaw-like configuration
- Basal cells arranged in anastomosing strands (plexiform pattern)
- Reverse polarity of basal columnar cells (a.k.a. Vickers-Gorlin change) with subnuclear vacuolization
- Central, loosely arranged stellate reticulum, which can become cystic

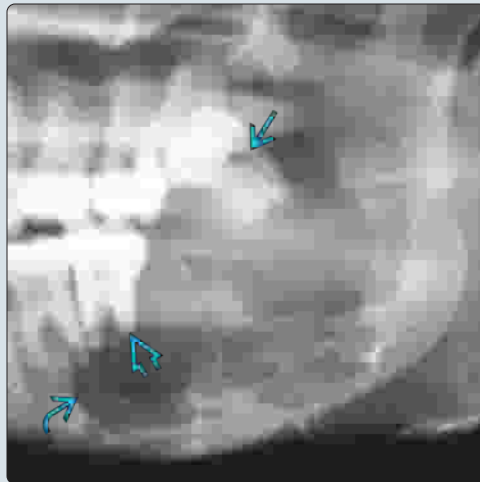
TOP DIFFERENTIAL DIAGNOSES

- Ameloblastic fibroma/ameloblastic fibro-odontoma
- Adenomatoid odontogenic tumor
- Calcifying odontogenic cystic tumor
- Ameloblastic carcinoma
- Malignant ameloblastoma
- Squamous odontogenic tumor

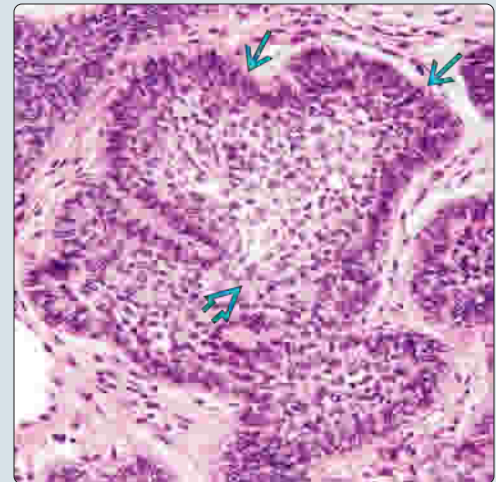
Large Ameloblastoma of the Mandible

(Left) Orthopantomograph of an ameloblastoma in the left posterior mandible with extreme displacement of the 3rd molar superiorly and root resorption of the 2nd molar. There is a well-defined periphery and multilocular appearance.

(Right) The follicular pattern is by far the most common and easily recognizable histologic variant of ameloblastoma. Even at this intermediate magnification the basal palisading and stellate reticulum are easily identified.

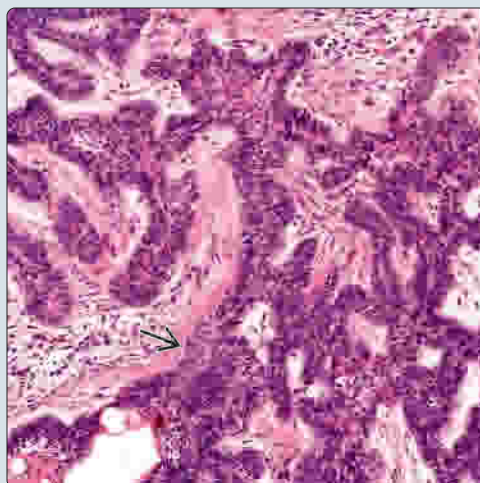


Follicular Variant of Ameloblastoma

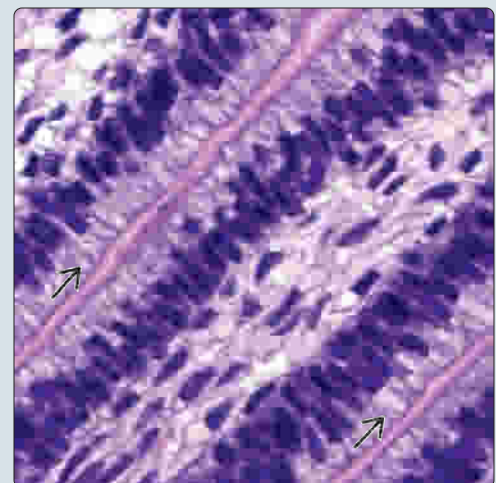


Plexiform Variant of Ameloblastoma

(Left) The plexiform variant is the 2nd most common histologic variant. It is characterized by anastomosing cords and islands of odontogenic epithelium, with only scant stellate reticulum identified. Reverse polarization is noted. **(Right)** Note the prominent reverse polarity of the nuclei. The columnar nuclei are set within tall cells, illustrating the subnuclear vacuolization. The vacuoles are lined up against fibrovascular cores. These findings are referred to as "Vickers-Gorlin" change.



Subnuclear Vacuolization



TERMINOLOGY**Definitions**

- Locally aggressive, benign, epithelial odontogenic neoplasm arising from remnants of odontogenic epithelium

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Most common odontogenic tumor, after odontomas
 - Incidence is equal to all other odontogenic tumors combined
 - Peripheral ameloblastoma is most common peripheral odontogenic tumor
- Age
 - Intraosseous
 - Wide age: 2nd-6th decades; mean: 36 years
 - Rare before 10 years
 - Unicystic
 - Tend to develop at younger age
 - 75% found in 2nd-3rd decades
 - Peripheral
 - Average: 51 years
- Sex
 - Equal distribution

Site

- 80-85% occur in posterior mandible
- Peripheral variant found within gingiva
 - Usually anterior mandible
- Uncommon in sinonasal tract

Presentation

- Usually asymptomatic
 - Oftentimes incidental findings on routine dental radiographs
- Painless swelling or jaw expansion
- Large lesions may present as disfiguring masses
- Pain is unusual

Treatment

- Surgical approaches
 - Conventional ameloblastomas generally require en bloc resection
 - Surgical margins extend at least 1 cm beyond radiographic evidence of tumor
 - Maxillary tumors may require more radical approach due to proximity of vital structures
 - Postsurgical reconstruction often needed
 - Unicystic lesions are treated with local enucleation
 - Peripheral lesions are easily treated with local excision
- Close clinical follow-up required for all ameloblastomas
- *BRAF*V600E inhibitor shows promise in future management

Prognosis

- Conventional ameloblastoma
 - Recurrence rate up to 35%
 - Persistent and infiltrating behavior
 - May kill patient by invading vital structures

- Particularly tumors of posterior maxilla
- Unicystic ameloblastoma
 - Recurrence rates of 5-10%
- Peripheral ameloblastoma
 - Recurrence rates up to 25%
 - Easily retreated with local excision
- Histologic subtypes do not affect prognosis
- Rare transformation to ameloblastic carcinoma
 - Locally invasive with poor survival
- Rarely undergoes transformation to malignant ameloblastoma
 - Associated with poor survival
 - Metastases: 75% lung
 - Less often: Liver, skull, brain, kidney

IMAGING**General Features**

- Conventional types usually appear as multilocular radiolucencies
 - Multilocular: Soap bubble or honeycomb appearance
- Unilocular or unicystic tumors lack loculations
- Often associated with impacted tooth; may cause tooth resorption
- Peripheral lesions may show some underlying erosion of bone; should not invade
- Desmoplastic variant usually appears as mixed radiopaque/radiolucent lesion
 - Oftentimes thought to be benign fibroosseous lesion
- Cortical expansion is frequent finding

MACROSCOPIC**General Features**

- Solid to cystic
- Small lesions may appear circumscribed
- Larger lesions will infiltrate or expand surrounding bone
- Unicystic lesions, by definition, must be grossly unicystic

Size

- Broad range: With potential for massive growth

Sections to Be Submitted

- Bone margins

MICROSCOPIC**Histologic Features**

- Blend of ameloblasts and epithelial cells trying to reduplicate enamel organ
- Ameloblastic cells are palisaded about periphery of tumor nests in jigsaw-like configuration
- Basal cells arranged in anastomosing strands (plexiform pattern)
- Reverse polarity of basal columnar cells (a.k.a. Vickers-Gorlin change) with subnuclear vacuolization
 - Nuclei displaced away from basement membrane and are hyperchromatic
- Central, loosely arranged stellate reticulum, which can become cystic
 - Cells can be spindle-shaped, basaloid, granular, or show squamous differentiation

- Invasive

Variants

- **Follicular**
 - Islands of odontogenic epithelium with peripheral palisading
 - Fibrous stroma
- **Plexiform**
 - Long, anastomosing cords or sheets of odontogenic epithelium
 - Peripheral palisading
 - Loose stroma
- **Acanthomatous**
 - Squamous metaplasia within odontogenic epithelial islands
- **Unicystic**
 - Tumor confined to luminal wall of single cyst
- **Desmoplastic**
 - Dense angular islands of odontogenic epithelium set in dense collagenous stroma
 - Peripheral palisading found only focally
- **Basal cell**
 - Nests of uniform basal cells lacking central stellate reticulum
- **Granular cell**
 - Central epithelial cells have granular eosinophilic cytoplasm

ANCILLARY TESTS

Genetic Testing

- *BRAFV600E* mutations have been identified
 - Diagnostic and prognostic implications
- *ING* family of tumor suppressor gene has high frequency loss of heterozygosity (LOH)
 - *ING5* locus LOH correlated to solid tumor type
- Notch signaling molecules may be associated with specific tumor phenotypes
- Dysregulation of a number of genes involved in normal tooth development may play role
 - *FOS* oncogene most overexpressed gene
 - Underexpressed genes include
 - *SHH*, *TRAF3*, *DCC*, *CDH12*, *TDGF1*, *TGFB1*
- Higher expression of p53 and MDM2 may correlate with aggressive behavior

DIFFERENTIAL DIAGNOSIS

Ameloblastic Fibroma

- Younger patients
- Mesenchymal stroma resembling dental papilla
 - Plump, stellate-shaped cells with loose matrix
- Epithelial component
 - Thin cords or strands
 - Small islands

Ameloblastic Fibro-odontoma

- Younger patients
- Resembles ameloblastic fibroma
- Mineralized tissue
 - Enamel matrix, dentin, cementum

Adenomatoid Odontogenic Tumor

- Favors anterior maxilla
- Encapsulated
- Duct-like spaces
- Nodular swirling pattern
- Amorphous amyloid-like material
- Calcifications

Calcifying Odontogenic Cystic Tumor

- Presence of ghost cells with calcifications

Ameloblastic Carcinoma

- More destructive growth
- Cytologic features of malignancy, including pleomorphism and increased mitotic activity

Malignant Ameloblastoma

- Requires development of metastatic deposits, usually lung

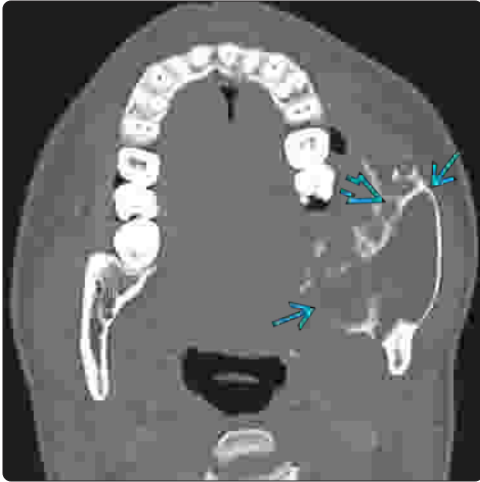
Squamous Odontogenic Tumor

- Rarely cystic
- Peripheral cells in epithelial islands do not show polarization

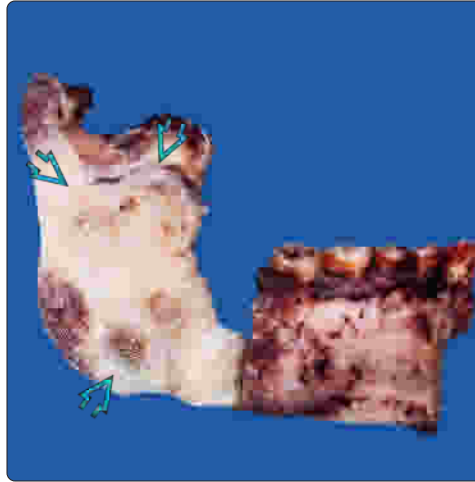
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Maxillary Ameloblastoma

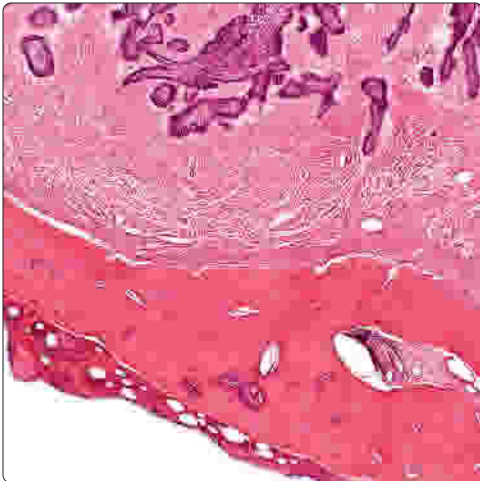


Ameloblastoma of Mandible

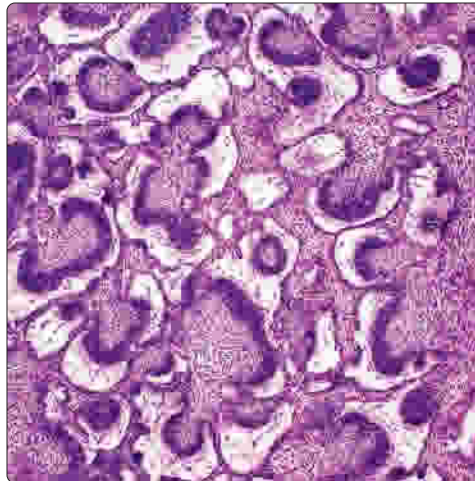


(Left) Axial bone CT shows expansion of the buccal and lingual cortices [1]. The characteristic thick septa between the lesion loculations are also evident [2]. (Right) Gross photograph shows a mandibular resection for an ameloblastoma. Surgical excision with at least 1 cm margins is the expectation. Tumor [3] is readily identifiable.

Positive Bone Margin

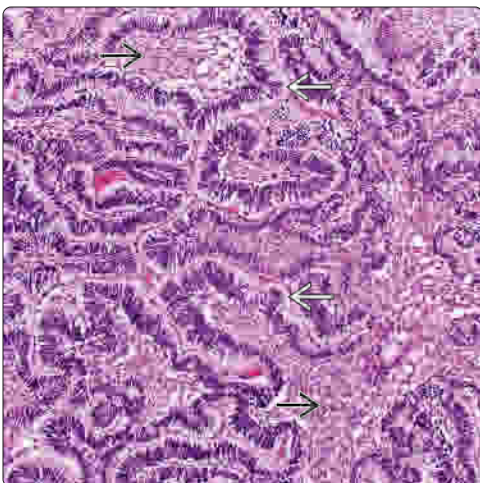


Ameloblastic Budding

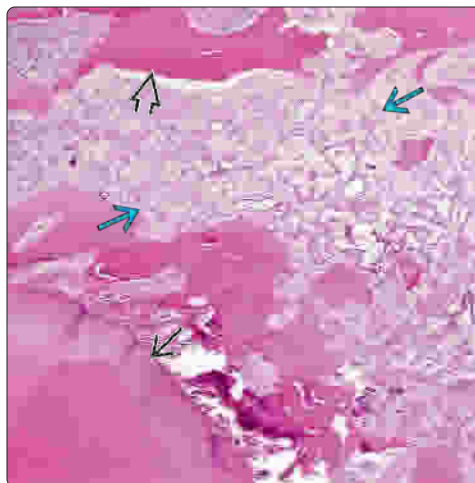


(Left) Hematoxylin and eosin shows tumor in a designated bone margin. Intraoperatively and radiologically, this margin was thought to be negative. Frozen sections are not practical on tissue containing bone, potentially delaying immediate reconstructive efforts. (Right) Classic palisading of the nuclei with typical reverse polarity and subnuclear clearing is seen in this ameloblastoma. The stellate reticulum has a syncytial architecture. Edema is focally noted.

Classical Ameloblastoma



Ameloblastoma Between Teeth and Bone



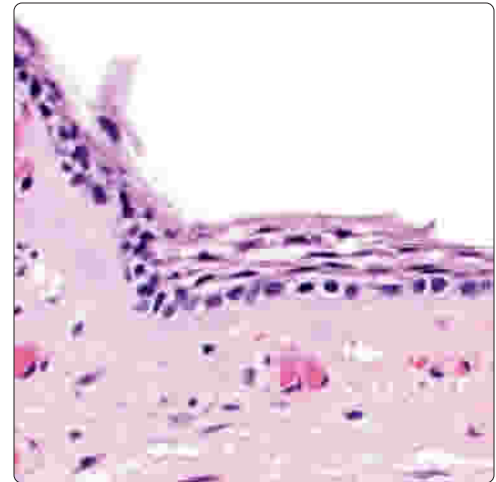
(Left) This micrograph demonstrates the classical features of an ameloblastoma. There is central stellate reticulum [1] surrounded by palisaded columnar cells with reverse polarization [2]. (Right) This hematoxylin and eosin shows an infiltrative ameloblastoma [3]. The tumor is seen destroying the adjacent bone [4]. Radiographically, the tooth [5] also showed signs of root resorption.

Unicystic Ameloblastoma

(Left) Radiographic image of a 21-year-old patient with a unicystic ameloblastoma. A diagnosis of unicystic ameloblastoma beyond the 2nd and 3rd decades should be made with caution, with multiple step sections reviewed to confirm the diagnosis. (Right) This unicystic ameloblastoma shows classic histologic features of any ameloblastoma but is confined to the cystic lining and shows a very thin lining. Correlation with radiographs and intraoperative reports is required with this variant.



Unicystic Ameloblastoma

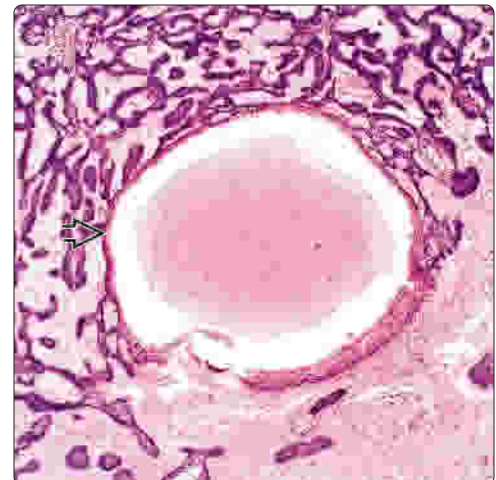


Multicystic Ameloblastoma

(Left) This gross photograph shows the multicystic appearance of a conventional ameloblastoma. These cystic spaces are usually seen on image studies as multiloculations. (Right) Cystic degeneration of a large solid tumor with a primarily plexiform histologic variant can be occasionally seen. Cyst formation is relatively uncommon in this histologic pattern and is instead more frequently seen in the follicular type.

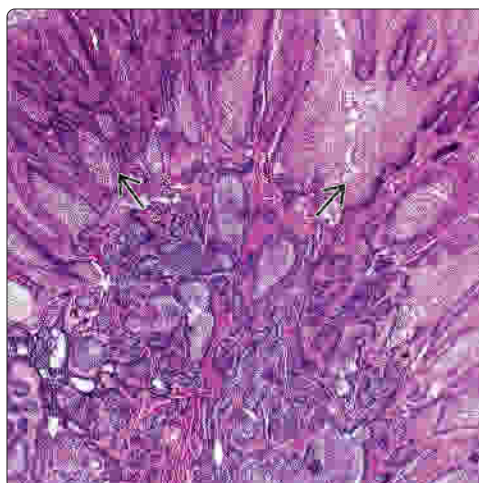


Cystic Degeneration



Surface Epithelium and Ameloblastoma

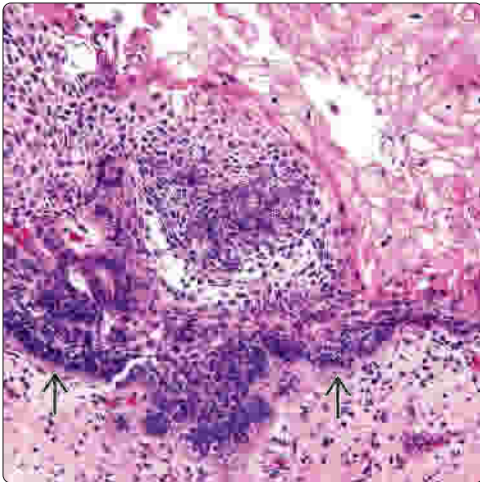
(Left) The surface epithelium is quite hyperplastic, overlying and blending with the ameloblastoma below. Nests and sheets of ameloblastic epithelium and stellate reticulum can be seen at this low power. (Right) This example of a peripheral ameloblastoma shows more subtle islands of epithelium below the surface. Care should be taken to ensure that this does not represent an intraosseous tumor with extension into the surrounding tissues.



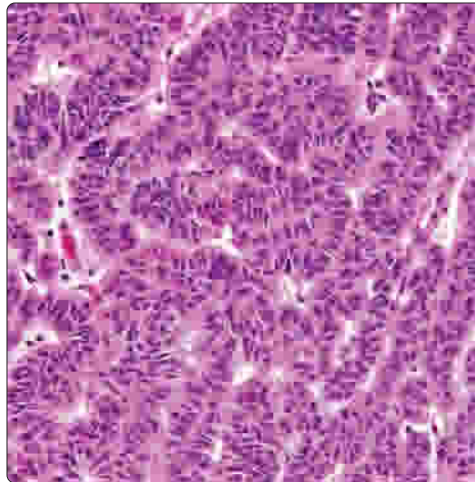
Peripheral Ameloblastoma



Acanthomatous Ameloblastoma

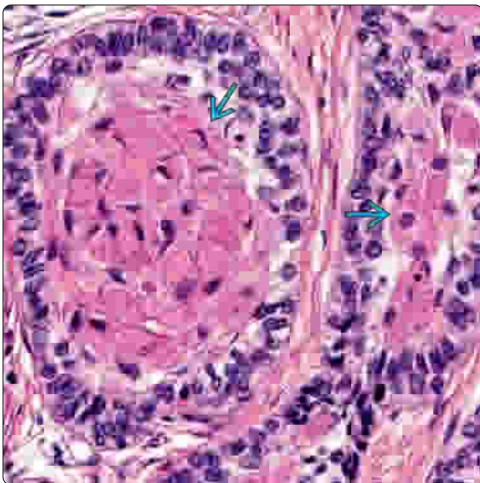


Basal Cell Variant

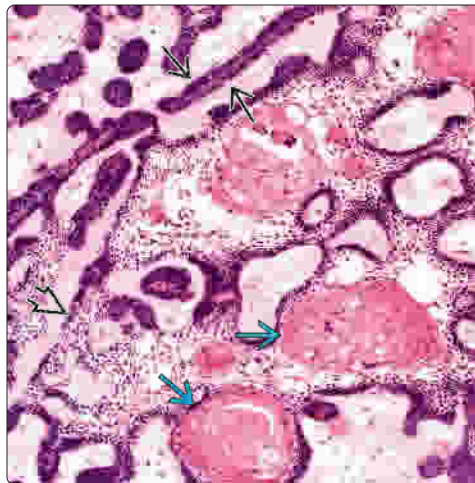


(Left) Columnar cells with peripheral palisading are seen. Note the stellate reticulum with keratinization. Squamous cell carcinoma and squamous odontogenic tumor are in the differential diagnosis. (Right) Hematoxylin and eosin shows the basal cell variant of ameloblastoma. Note the cuboidal, peripheral cells with nuclei that show hyperchromasia and lack of stellate reticulum. The basal cell type is the least common variant of ameloblastoma and can be a diagnostic challenge.

Granular Cell Variant



Acanthomatous Variant



(Left) Hematoxylin and eosin shows the granular variant of ameloblastoma. Note the prominent granular cytoplasm of the cells within the islands. Like other variants, characteristic areas may be found only in part of the tumor. (Right) Many tumors will have multiple patterns as seen in tumor with areas of plexiform, acanthomatous, and follicular patterns. While the different variants of ameloblastoma must be recognized to ensure proper diagnosis, the prognosis among variants is generally the same.

Desmoplastic Ameloblastoma



Desmoplastic Ameloblastoma



(Left) Radiograph shows a desmoplastic ameloblastoma, characterized by a mixed radiolucent and radiopaque appearance. In addition to having a unique radiographic presentation, they also have a predilection for the maxilla, while other variants favor the mandible. (Right) Hematoxylin and eosin shows the desmoplastic variant of ameloblastoma. The islands of odontogenic epithelium appear squeezed by the dense collagenous stroma. The classic Vickers-Gorlin changes are difficult to see or are absent.

KEY FACTS

TERMINOLOGY

- Benign odontogenic neoplasm of squamous epithelium that may demonstrate locally aggressive behavior

CLINICAL ISSUES

- Very rare
- Conservative removal of lesion and any affected teeth
- Rarely recur
- Anterior maxilla > posterior mandible
- Localized loosening of teeth in absence of periodontal disease

IMAGING

- Not specific but usually consist of triangular radiolucent defect lateral to tooth

MACROSCOPIC

- Gross specimen may consist of fragmented curettings and fragments of bone

MICROSCOPIC

- Epithelial nests and islands
 - Variable shapes and sizes
 - Cytologically bland with intercellular bridges
 - Single cell keratinization may be seen
- Stroma
 - Fibrous connective tissue
- Hyalinization may be seen around islands
- Laminated microcalcifications

TOP DIFFERENTIAL DIAGNOSES

- Ameloblastoma
- Squamous cell carcinoma
- Metastatic carcinoma
- Odontogenic epithelial rests
- Organ of Chievitz

(Left) Bitewing radiograph reveals a triangular radiolucent defect between the premolar and canine. This example was treated as periodontal disease but failed to respond, so it was subsequently biopsied. (Right) This low-power H&E shows a SOT composed predominantly of cord-like nests of bland squamous epithelium. Squamous cell carcinoma may still be in the differential diagnosis for this tumor, but a high-power view will show a lack of cytologic atypia. Note the fibrous stroma.

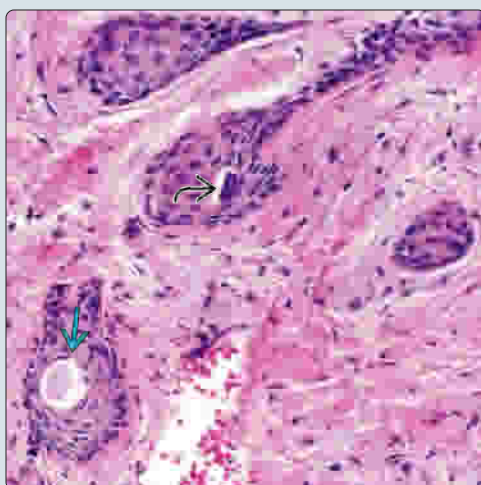
Triangular Radiolucency Between Teeth



Cord-Like Nests of Squamous Epithelium

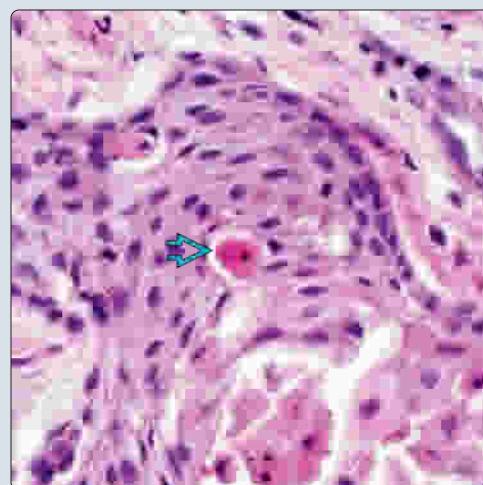


Microcyst and Calcification in Squamous Odontogenic Tumor



(Left) This medium-power H&E shows nests of bland odontogenic epithelium found in a squamous odontogenic tumor. In this field, a microcyst and a fragment of a laminated calcification can be seen. (Right) This high-power H&E of an island of epithelium consists of cells of varying sizes. Note the single cell keratinization that is not uncommonly seen in squamous odontogenic tumors.

Single Cell Keratinization in Squamous Odontogenic Tumor



TERMINOLOGY

Abbreviations

- Squamous odontogenic tumor (SOT)

Definitions

- Benign odontogenic neoplasm of squamous epithelium that may demonstrate locally aggressive behavior

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Believed to arise from rest of Malassez in periodontal ligament
- Peripheral lesions may arise from surface epithelium
- SOT-like proliferation has been reported in other odontogenic cysts

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very rare
- Age
 - Wide range: 2nd-7th decades

Site

- Anterior maxilla > posterior mandible
- Rarely reported as peripheral lesion in gingiva

Presentation

- Localized loosening of teeth in absence of periodontal disease
 - Deep periodontal pocket
- Gingival swelling
- Pain
- Asymptomatic
 - Incidental finding on routine dental radiographs
- Rarely multifocal
- Associated teeth generally test vital

Treatment

- Surgical approaches
 - Conservative removal of lesion and any affected teeth
 - Aggressive curettage of affected bone
 - Scaling and root planing of adjacent teeth
 - Prosthetic restoration of extracted teeth
 - Peripheral lesions may be excised down to periosteum

Prognosis

- Rarely recur
- Maxillary lesions may require closer follow-up as they have been reported to be more aggressive
 - Anatomy of region
 - Porous bone makes removal difficult
- Multifocal lesions have been reported as less aggressive
- Very rare cases of malignant transformation

IMAGING

Radiographic Findings

- Nonspecific but usually consist of triangular radiolucent defect lateral to tooth

- May suggest loss of bone from periodontal disease
- Ill- and well-defined radiolucency
- Sclerotic margins
- Occasional cortical erosion
- May occasionally displace adjacent teeth

MACROSCOPIC

General Features

- Gross specimen may consist of fragmented curettings and fragments of bone

MICROSCOPIC

Histologic Features

- Epithelial nests and variably shaped islands
 - Bland cytology with intercellular bridges
 - Single cell keratinization may be seen
 - Microcysts within cellular islands
 - Laminated microcalcifications
- Stroma
 - Fibrous connective tissue
 - Hyalinization may be seen around islands

DIFFERENTIAL DIAGNOSIS

Ameloblastoma

- Much more common
- More destructive, radiolucent lesion
- Peripheral palisading nuclei, reverse polarization
- Stellate reticulum in the center

Squamous Cell Carcinoma

- Frequently, may have soft tissue component
- Cytologically atypical, including atypical mitotic figures

Metastatic Carcinoma

- History of primary disease
- Cytologically atypical, with desmoplastic stroma

Odontogenic Epithelial Rests

- Small collections of odontogenic epithelium
- Usually found incidentally in other conditions
 - Dental follicular tissue
 - Dentigerous cysts
 - Other odontogenic cyst and tumors

Organ of Chievitz

- a.k.a. juxtaoral organ of Chievitz
- Most commonly found in retromolar pad area
- Collection of discrete nest of cells with distinct squamous appearance

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KEY FACTS

TERMINOLOGY

- Benign epithelial odontogenic neoplasm with local invasion, characterized by amyloid-like material and tendency to calcify
- Pindborg tumor

CLINICAL ISSUES

- Rare
- ~ 66% in mandible (body/posterior)
- Peripheral variant excised to periosteum
- Local resection, including narrow rim of bone
- Recurrence rate: 15%
- Long-term follow-up recommended

IMAGING

- Unilocular radiolucency
- Considerable variation of mixed radiolucent-radiopaque lesions
- Associated with impacted tooth in > 50% of cases

MACROSCOPIC

- Solid tumor (no cyst formation)
- Varying amounts of calcifications

MICROSCOPIC

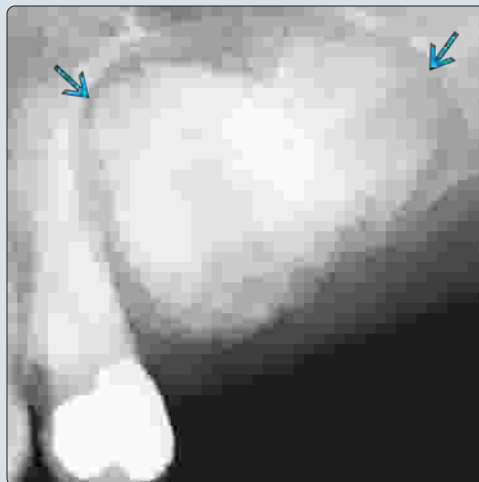
- Sheets, cords, or islands of polyhedral epithelial cells
- Abundant eosinophilic cytoplasm with prominent cell borders and intercellular bridges
- Hyalinized, eosinophilic homogeneous stroma: Amyloid
- Liesegang rings: Basophilic concentric calcified layers
- Clear cell variant uncommon

TOP DIFFERENTIAL DIAGNOSES

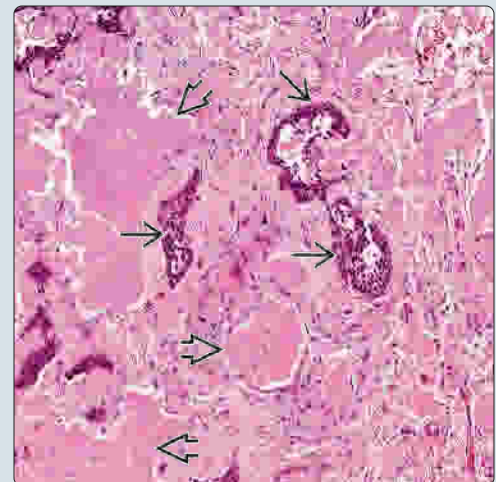
- Squamous cell carcinoma
- Clear cell odontogenic carcinoma
- Metastatic tumors
 - Squamous cell carcinoma
 - Clear cell renal cell carcinoma

Primarily Radiopaque Calcifying Epithelial Odontogenic Tumor

(Left) Bitewing radiograph shows a sclerotic lesion with fluffy calcification and a lucent margin. No impacted tooth was present in this patient. (Courtesy C. Dunlap, MD.) (Right) Low-power view shows islands of polyhedral epithelial cells in a fibrous stroma. Areas of amorphous, eosinophilic, amyloid-like material are readily identifiable in this tumor. This low-power H&E should elicit consideration of squamous cell carcinoma and metastatic carcinoma, part of the differential diagnoses for CEOT.



Epithelial Islands in Fibrous Stroma

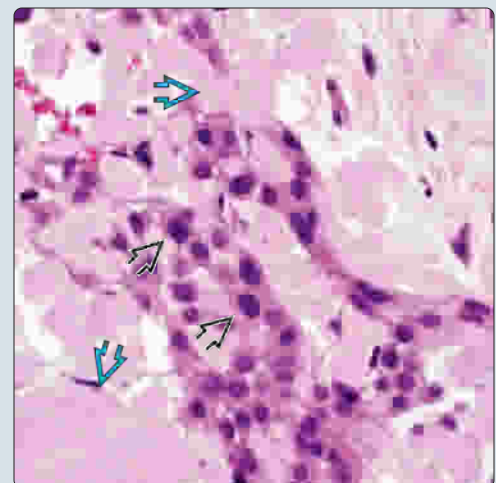


Calcifications Within Sheets of Squamous Cells

(Left) This high-power H&E shows the characteristic calcifications of a CEOT. Note the basophilic concentric layers immediately adjacent to tumor cells with abundant eosinophilic cytoplasm and well developed intercellular bridges. (Right) In this high-power H&E, the polyhedral tumor cells are easily identified in close association with the eosinophilic, acellular, homogenous, extracellular amyloid-like stroma.



Cords of Tumors Cells With Amyloid Stroma



TERMINOLOGY

Abbreviations

- Calcifying epithelial odontogenetic tumor (CEOT)

Synonyms

- Pindborg tumor

Definitions

- Benign epithelial odontogenic neoplasm with local invasion, characterized by amyloid-like material and tendency to calcify
- Benign epithelial odontogenic tumor that secretes amyloid protein, which tends to calcify

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare; < 1% of all odontogenic tumors
- Age
 - Wide range: 20-60 years most common; mean: 40 years
 - Male patients present ~ 1 decade earlier than female patients
- Sex
 - Equal gender distribution

Site

- Vast majority are intraosseous
 - ~ 66% arise in mandible
 - Usually posterior: Molar or premolar area (body)
 - Remainder arise in maxilla (33%)
- Extraosseous: Peripheral variant
 - ~ 5% of cases, involving anterior gingiva

Presentation

- Asymptomatic, painless expansile mass
- Slowly growing swelling
- Firm, painless mass on gingiva

Treatment

- Surgical approaches
 - Local resection, including narrow rim of bone
 - Peripheral variant excised to periosteum

Prognosis

- Recurrence rate: 15%
 - Slightly higher in clear cell variant (22%)
- Long-term follow-up recommended
- Malignant transformation is rare

IMAGING

Radiographic Findings

- Wide variation of mixed radiolucent-radiopaque lesion
- Unilocular or multilocular radiolucency
- Contains calcifications, aggregate around crown of unerupted teeth
- Associated with impacted tooth in > 50% of cases
 - Most common mandibular 3rd molar
- Peripheral variant may show cupping of underlying bone

MACROSCOPIC

General Features

- Solid, noncystic tumor, with varying amounts of calcification

Sections to Be Submitted

- Bone margins

MICROSCOPIC

Histologic Features

- Epithelial cells
 - Sheets, cords, or islands of cells
 - Polyhedral cells with abundant eosinophilic cytoplasm
 - Prominent, well-defined cell borders and intercellular bridges
 - Pleomorphism usually present
 - Giant tumor nuclei occasionally seen
 - Mitotic figures rare
 - Clear cell variant is uncommon
- Matrix (amyloid material)
 - Small, rounded to irregular homogenous masses of lightly eosinophilic hyaline material
 - Fibrous connective tissue
- Calcification of matrix material
 - Liesegang rings: Basophilic concentric layers
 - Usually adjacent to tumor cells
 - Noncalcifying variant is reported
- Rarely associated with adenomatoid odontogenic tumor

ANCILLARY TESTS

Histochemistry

- Amyloid matrix (+) with Congo red and thioflavin T

DIFFERENTIAL DIAGNOSIS

Squamous Cell Carcinoma

- Lacks amyloid and calcifications; greater pleomorphism

Clear Cell Odontogenic Carcinoma

- Lacks amyloid and calcifications

Metastatic Tumors

- **Squamous cell carcinoma**
 - Primary site must be identified
 - Lacks amyloid and calcifications; greater pleomorphism
- **Clear cell renal cell carcinoma**
 - Primary site must be identified
 - Vascular pattern with extravasated erythrocytes
 - Lacks amyloid and calcifications
 - **Positive:** Pax-2, CD10, renal cell carcinoma marker

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2. Murphy CL et al: Odontogenic ameloblast-associated protein nature of the amyloid found in calcifying epithelial odontogenic tumors and unerupted tooth follicles. *Amyloid.* 15(2):89-95, 2008
3. Shekarkhar MJ et al: Cytologic findings in calcifying epithelial odontogenic tumor: a case report. *Acta Cytol.* 49(5):533-6, 2005

KEY FACTS

TERMINOLOGY

- Benign tumor of odontogenic epithelium with distinct duct-like appearance

CLINICAL ISSUES

- Most common in 2nd decade
- Female > male (2:1)
- Most common in anterior maxilla
- Associated with unerupted teeth
- Enucleation from bone
- Recurrences are exceedingly rare to nonexistent

IMAGING

- Well-defined radiolucency, usually unilocular
- Often associated with unerupted tooth, usually the maxillary canine
- May contain fine calcifications, "snow flakes"

MACROSCOPIC

- Usually surrounded by thick, well-defined capsule
- Usually < 3 cm

MICROSCOPIC

- Duct-like nests or cords lined by cuboidal to columnar cells
- Reversed nuclear polarity away from central lumen-like space
- Duct-like spaces are pseudolumina containing eosinophilic secretions
- Contains amorphous amyloid-like material and mineralizations

TOP DIFFERENTIAL DIAGNOSES

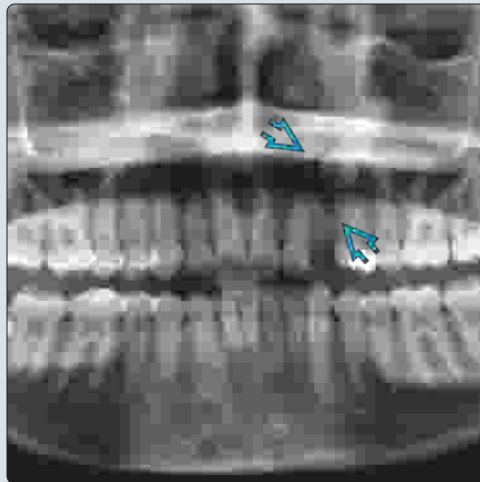
- Ameloblastoma
- Salivary gland Tumors

DIAGNOSTIC CHECKLIST

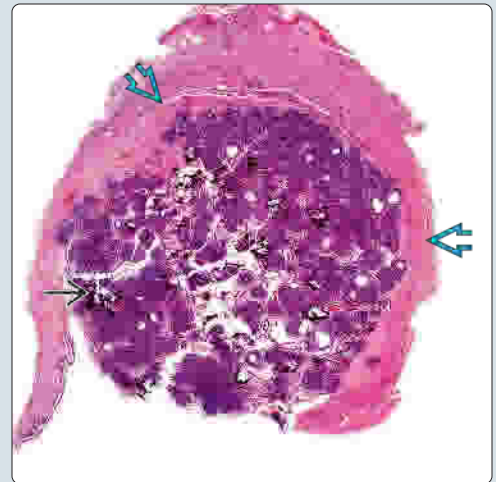
- 2/3 women, occur in the 2nd decade, develop in middle third of anterior maxilla, associated with impacted tooth

Classic Finding of AOT

(Left) This particular AOT follows the "2/3 rule" in this 19-year-old woman, and the tumor is found in the maxilla in association with an impacted canine. No calcifications are seen. A dentigerous cyst is also included in the differential diagnosis. (Right) Low-power view demonstrates a thick capsule surrounding the tumor. It is this capsule that makes treatment relatively easy with enucleation. Mineralization (calcifications) can be seen throughout the specimen.

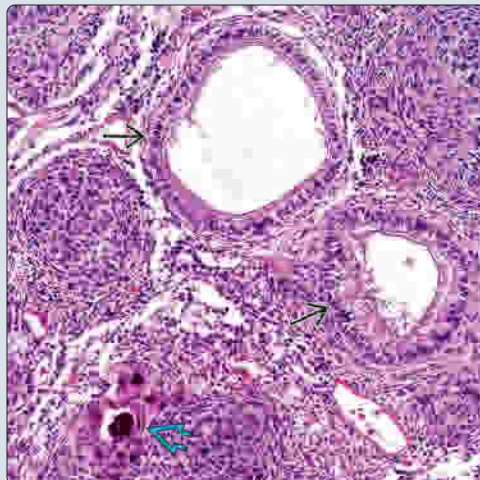


Well-Defined Capsule and Calcifications

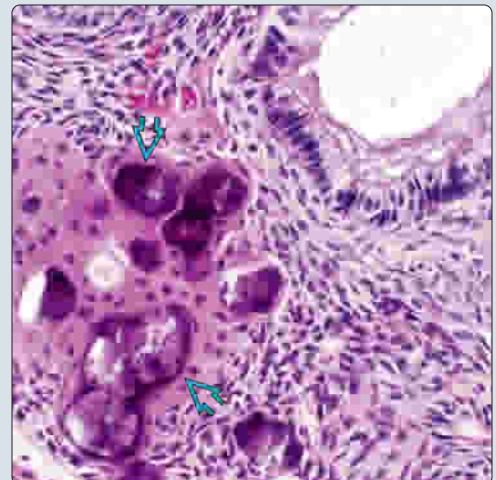


Gland-Like Structures, Cellular Stroma

(Left) H&E-stained tissue shows duct-like spaces lined by columnar cells demonstrating reverse nuclear polarity away from the central lumen space. This is also a feature of ameloblastoma, which is in the differential diagnosis. Note the focal calcifications. (Right) H&E shows an area of calcification with distinct laminations adjacent to a duct-like structure. These calcifications will often times appear as flake-like calcifications on image studies.



Calcifications in AOT



TERMINOLOGY

Abbreviations

- Adenomatoid odontogenic tumor (AOT)

Synonyms

- Formerly known as adenoameloblastoma
 - Confusion with ameloblastoma should be avoided

Definitions

- Benign tumor of odontogenic epithelium with distinct duct-like appearance embedded in mature connective tissue stroma

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- May derive from epithelium of enamel organ

CLINICAL ISSUES

Epidemiology

- Incidence
 - 3-7% of odontogenic tumors
- Age
 - Most common in 2nd decade: > 90% found before age 30
- Sex
 - Female > male (2:1)

Site

- Most common in anterior maxilla
- Rare extraosseous variant: Gingiva, favors maxilla

Presentation

- Usually asymptomatic
- Painless expansion of bone and displacement of adjacent teeth
 - Increased age is associated with increase in signs and symptoms
- Usually associated with unerupted teeth
- Extraosseous variants
 - Small, sessile
 - May be ulcerated due to secondary trauma
- May occasionally be seen in association with calcifying epithelial odontogenic tumor

Treatment

- Enucleation achieves excellent result
- Orthodontics to correct malocclusion, if present

Prognosis

- Recurrences are exceedingly rare to nonexistent

IMAGING

Radiographic Findings

- Well-defined radiolucency, usually unilocular
- Often associated with unerupted tooth
 - Usually maxillary canine
- May contain fine calcifications, "snow flakes"

MACROSCOPIC

General Features

- Usually surrounded by thick, well-defined capsule
- Cut section may reveal
 - Cysts or solid pattern
 - Calcifications
 - Unerupted tooth

Size

- Usually < 3 cm
- Size appears to correlate with increased age

MICROSCOPIC

Histologic Features

- Nodules of odontogenic epithelium
 - Duct-like nests or cords lined by cuboidal to columnar cells
 - Reversed nuclear polarity away from central lumen-like space
 - Duct-like spaces are pseudolumina containing eosinophilic secretions
- Stroma
 - Spindle to polyhedral eosinophilic cells
 - Swirling to nodular pattern
 - Contains amorphous amyloid-like material (tumor droplets)
 - Mineralizations
 - Small vessels
- Melanin pigmentation of both odontogenic and stromal cells has been described

DIFFERENTIAL DIAGNOSIS

Ameloblastoma

- Lacks gland-like structures, has stellate reticulum
- Usually larger and more invasive
- Lacks capsule

Salivary Gland Tumors

- Rare location, usually without calcifications
- Lacks reverse polarity and stroma is not prominent

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Tumor of 2/3: 2/3 women, occur in 2nd decade, develop in middle 1/3 of anterior maxilla, associated with impacted tooth

SELECTED REFERENCES

1. Becker T et al: Critical evaluation of the radiological and clinical features of adenomatoid odontogenic tumour. *Dentomaxillofac Radiol.* 41(7):533-40, 2012
2. Ide F et al: Development and growth of adenomatoid odontogenic tumor related to formation and eruption of teeth. *Head Neck Pathol.* 5(2):123-32, 2011
3. Philipsen HP et al: An updated clinical and epidemiological profile of the adenomatoid odontogenic tumour: a collaborative retrospective study. *J Oral Pathol Med.* 36(7):383-93, 2007
4. Philipsen HP et al: Adenomatoid odontogenic tumour: facts and figures. *Oral Oncol.* 35(2):125-31, 1999

KEY FACTS

TERMINOLOGY

- Ameloblastic fibroma (AF): Benign true mixed tumor composed of odontogenic ectomesenchyme (dental papilla-like) and epithelial tissue resembling odontogenic epithelium without dental hard tissues
- Ameloblastic fibro-odontoma (AFO): Mixed odontogenic lesion containing dentin and enamel

CLINICAL ISSUES

- First 2 decades of life
- Mandible to maxilla ratio is 3.3:1, with posterior location most common > anterior jaws
- AF
 - Recurrence is variable
 - Uncommon malignant transformation (~ 10%) to ameloblastic fibrosarcoma
- AFO
 - Recurrences have not been documented

IMAGING

- Radiolucent
- AFO has variable amounts of calcified materials

MICROSCOPIC

- Composed of small islands, cords, or strands of odontogenic epithelium
- Stroma resembles dental papilla of embryologic tooth development
- Mineralized tissue in AFO only
 - Enamel, dentin, calcified material
- High mesenchymal Ki-67 in recurrent/malignant AF

TOP DIFFERENTIAL DIAGNOSES

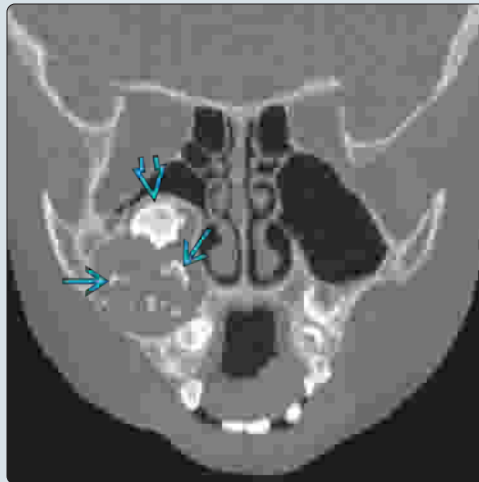
- Ameloblastoma, odontoma, ameloblastic fibrosarcoma

DIAGNOSTIC CHECKLIST

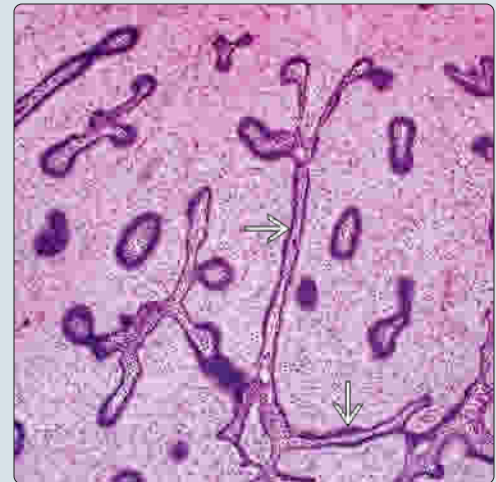
- Odontoma part of AFO may not be submitted for microscopic review: Do not diagnosis it as AF only

Maxilla Ameloblastic Fibro-Odontoma With Flocculent Calcifications

(Left) Coronal bone CT reveals a lucent lesion with central flocculent calcifications and a displaced unerupted tooth. Note that this lesion only appears cystic on CT. A circumscribed soft tissue mass containing calcifications was encountered at surgery. (Right) Hematoxylin and eosin shows long, narrow cords of odontogenic epithelium. The stroma is a loose matrix that resembles the dental papilla of a developing tooth, showing low cellularity.

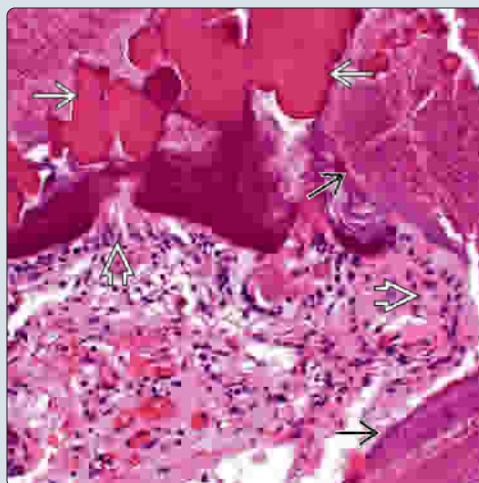


Narrow Cords of Epithelium

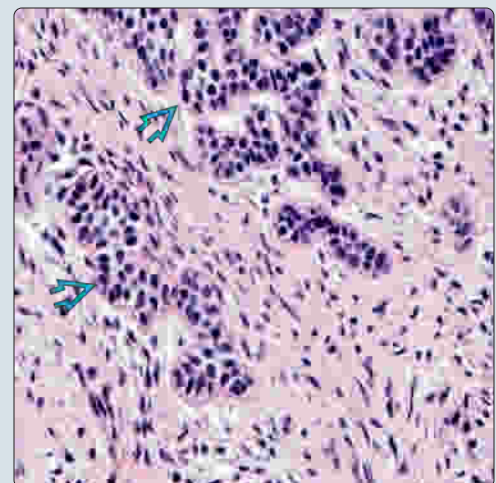


Odontogenesis Products in Odontoma

(Left) This ameloblastic fibro-odontoma (AFO) shows mature dentin and calcified material in close relationship to odontogenic epithelium. Lesions with well-formed odontomas may not have the mineralized portion submitted for microscopic analysis, requiring careful review of the gross description to ensure the case is not erroneously diagnosed as an ameloblastic fibroma (AF), rather than an AFO. (Right) Small islands and cords of odontogenic epithelium are set within a cellular stroma.



Small Discrete Islands of Epithelium



TERMINOLOGY

Abbreviations

- Ameloblastic fibroma (AF)
- Ameloblastic fibro-odontoma (AFO)

Definitions

- Ameloblastic fibroma
 - Benign true mixed tumor composed of odontogenic ectomesenchyme (dental papilla-like) and epithelial tissue resembling odontogenic epithelium without dental hard tissues
- Ameloblastic fibro-odontoma
 - Tumor composed of mixture of odontogenic epithelial and mesenchymal tissues that also contains dentin and enamel

ETIOLOGY/PATHOGENESIS

Distinctive Entities

- Ultrastructural and immunohistochemical findings differ
- AFOs actually occur, on average, at slightly younger age than AF contradicting theory that AF become AFOs

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare; ~ 3% of all odontogenic tumors
- Age
 - 80% develop in first 2 decades of life; rare in adults
- Sex
 - AF: Slight male predilection (1.4:1); AFO: Equal gender distribution

Site

- Posterior mandible is most common location > posterior maxilla, anterior jaws
- Mandible to maxilla ratio is 3.3:1

Presentation

- Small lesions: Usually asymptomatic, slow growing found on routine radiographs
- Larger lesions: Swelling, may prevent eruption of teeth

Treatment

- Surgical approaches
 - Radical vs. conservative management depends on age

Prognosis

- AF
 - Recurrence is variable
 - Uncommon malignant transformation (~ 10%) to ameloblastic fibrosarcoma
 - ~ 50% of ameloblastic sarcomas develop in association with recurrent ameloblastic fibromas
 - Close follow-up is indicated
- AFO: Recurrences not reported

IMAGING

Radiographic Findings

- Radiolucent

- Unilocular or multilocular
- Well-circumscribed to sclerotic margin
- Frequently associated with unerupted tooth
- AFO will have variable amounts of calcified material: Flake-like or solid dense masses

MACROSCOPIC

Ameloblastic Fibroma

- White to tan, translucent

Ameloblastic Fibro-Odontoma

- White to tan, translucent
- Mineralized tooth structure

MICROSCOPIC

Histologic Features

- Epithelial component
 - Small islands, cords, or strands of odontogenic epithelium
 - Peripheral cells are columnar and ameloblast-like
 - Scant central areas of stellate reticulum-like tissue
- Stroma
 - Cellular, myxoid tissue resembling developing dental papilla
 - Cytologically bland round to angulated cells
- Mineralized tissue: AFO only
 - Enamel, dentin, calcified material

ANCILLARY TESTS

Immunohistochemistry

- Increased Ki-67 in mesenchyme of recurrent/malignant AF

DIFFERENTIAL DIAGNOSIS

Ameloblastoma

- Variable patterns, with loose to collagenous stroma

Odontoma

- Small odontogenic epithelial rests within normal dental follicular tissue
- No epithelium strands or pale myxoid stroma

Ameloblastic Fibrosarcoma

- Hypercellular stroma with increased mitoses

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Odontoma part of AFO may not be submitted for microscopic review; do not diagnosis it as AF in error

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2. Pontes HA et al: Report of four cases of ameloblastic fibro-odontoma in mandible and discussion of the literature about the treatment. J Craniomaxillofac Surg. 40(2):e59-63, 2012
3. Abughazaleh K et al: Peripheral ameloblastic fibroma of the maxilla: report of a case and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 105(5):e46-8, 2008

KEY FACTS

TERMINOLOGY

- Hamartomas of odontogenic epithelium and ectomesenchyme

CLINICAL ISSUES

- Most occur during first 2 decades of life
- Vast majority are asymptomatic
- Usually detected on routine dental radiographs
- Most common in maxilla
- Simple surgical excision
 - Complete removal of associated soft tissue

IMAGING

- Radiographic characteristics are considered diagnostic
- **Compound**
 - Tooth-shaped structures
 - Surrounded by radiolucent zone
- **Complex**
 - Radiodense mass

- Surrounded by radiolucent zone

MACROSCOPIC

- Tooth-shaped hard tissues
- Disorganized mass of white-yellow hard tissues

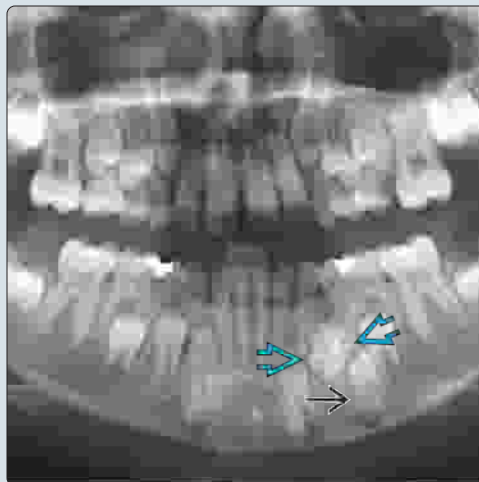
MICROSCOPIC

- Dentin, enamel matrix, cementum, and pulp tissue
- **Compound** odontomas: Organized architecture, recapitulating normal teeth
- **Complex** odontomas: Haphazard arrangement
- May be found in conjunction with other odontogenic cysts or tumors

TOP DIFFERENTIAL DIAGNOSES

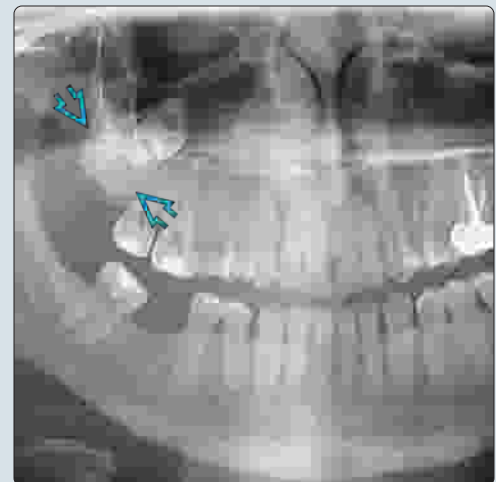
- Hyperdontia
- Root tip
- Impacted tooth

Compound Odontoma of Mandible

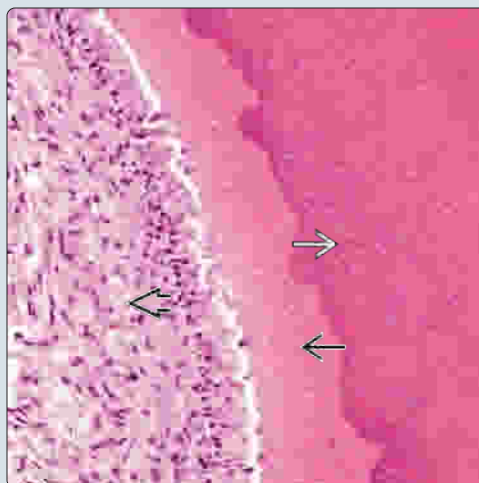


(Left) This compound odontoma [A] was found on a routine radiograph. Note the numerous tooth-shaped structures as well as the radiolucent rim. While asymptomatic, the odontoma likely would have eventually impeded the normal eruption of the mandibular 1st premolar [B]. (Right) Complex odontoma of the posterior mandible [C] shows a mixed mineralized mass without a well-formed tooth structure.

Complex Odontoma of Maxilla

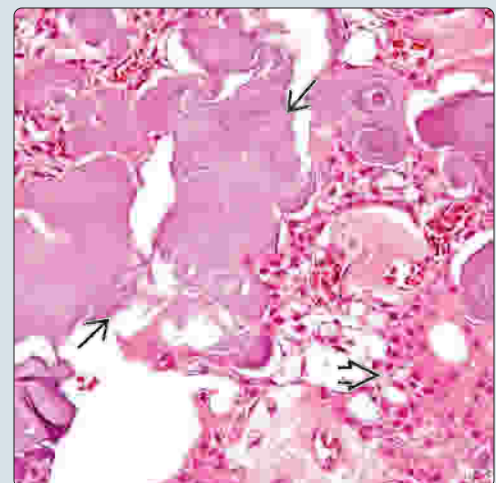


Organized Dentin Pulp Architecture



(Left) H&E shows the loose matrix that makes up the pulp tissue [A] of this odontoma. Immediately adjacent is the pre-dentin [B] and mature mineralized dentin [C]. This microscopic anatomy recapitulates normal tooth anatomy. (Right) H&E shows a focus of disorganized enamel matrix [D] and odontogenic epithelium [E] characteristic of a complex odontoma. Complex odontomas are more common in the posterior mandible.

Complex Odontoma



TERMINOLOGY

Definitions

- Hamartomas of odontogenic epithelium and ectomesenchyme

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Hamartoma
 - Compound odontoma
 - Small, tooth-like structures
 - Complex odontoma
 - Haphazard aggregate of enamel and dentin
 - Combination

CLINICAL ISSUES

Epidemiology

- Age
 - Most occur during first 2 decades of life
- Sex
 - Equal gender distribution

Site

- Most common in maxilla
 - Compound odontomas are most frequent in anterior maxilla
 - Complex odontomas are most frequent in posterior mandible

Presentation

- Usually detected on routine dental radiographs
- Vast majority are asymptomatic
- May prevent eruption of normal dentition
- Rarely, may erupt
- Rarely, may cause bone expansion
- May be part of syndrome (Rubinstein-Taybi)

Treatment

- Simple surgical excision
 - Complete removal of associated soft tissue
 - Dental follicular tissue/dentigerous cyst

Prognosis

- Excellent, without recurrence

IMAGING

Radiographic Findings

- Radiographic characteristics are considered diagnostic
- Compound
 - Tooth-shaped structures
 - Surrounded by radiolucent zone
- Complex
 - Radiodense irregular mass
 - Surrounded by radiolucent zone

MACROSCOPIC

General Features

- Compound

- Tooth-shaped hard tissues and associated fibrous connective tissue

- Complex
 - Disorganized mass of white-yellow hard tissues and associated fibrous connective tissue

Size

- Generally do not exceed size of normal tooth
- Rarely, up to 6 cm

MICROSCOPIC

Histologic Features

- **Compound odontomas** have architecture similar to normal tooth
 - Mature tubular dentin
 - Enamel matrix, mature enamel is lost during decalcification process
 - Cementum
 - Pulp tissue
 - Dental follicular tissue
 - Occasional dentigerous cyst
- **Complex odontomas** have haphazard arrangement
 - Haphazardly arranged tubular dentin
 - Dentin often surrounds islands of enamel/matrix
 - Thin layer of cementum may surround mass
 - Epithelial ghost cells are frequently seen
 - Dental follicular tissue
 - Occasional dentigerous cyst
- May be found in conjunction with other odontogenic cysts or tumors

DIFFERENTIAL DIAGNOSIS

Hyperdontia (Supernumerary Teeth)

- Complete, well-formed tooth, usually in males
- Rarely, syndrome associated
 - Gardner, Sturge-Weber, cleidocranial dysplasia

Root Tip

- History of incomplete tooth extraction
- May be symptomatic

Impacted Tooth

- Normal part of dentition

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Most common odontogenic tumor

SELECTED REFERENCES

1. An SY et al: Odontoma: a retrospective study of 73 cases. *Imaging Sci Dent.* 42(2):77-81, 2012
2. Soluk Tekkesin M et al: Clinical and histopathological investigation of odontomas: review of the literature and presentation of 160 cases. *J Oral Maxillofac Surg.* 70(6):1358-61, 2012
3. da Silva LF et al: Odontomas: a clinicopathologic study in a Portuguese population. *Quintessence Int.* 40(1):61-72, 2009
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5. Hidalgo-Sánchez O et al: Metaanalysis of the epidemiology and clinical manifestations of odontomas. *Med Oral Patol Oral Cir Bucal.* 13(11):E730-4, 2008

KEY FACTS

TERMINOLOGY

- Rare, benign, odontogenic neoplasm of inactive-appearing odontogenic epithelium embedded in mature fibrous stroma

ETIOLOGY/PATHOGENESIS

- Considered to be of periodontal ligament origin

CLINICAL ISSUES

- Uncommon
- Wide age range; mean: 40 years
- Female > male (3:1)
- Asymptomatic, detected on routine dental radiographs
 - Variable size, but usually < 3 cm
- Symptomatic
 - Swelling, loosening of teeth, mild pain to painless, draining
 - Lesions of anterior maxilla may have a palatal bony depression

- Occasionally creates characteristic cleft

- Treated by enucleation or curettage

IMAGING

- Unilocular or multilocular radiolucent lesions
- Frequently associated with unerupted tooth
- Expansion of affected bone

MICROSCOPIC

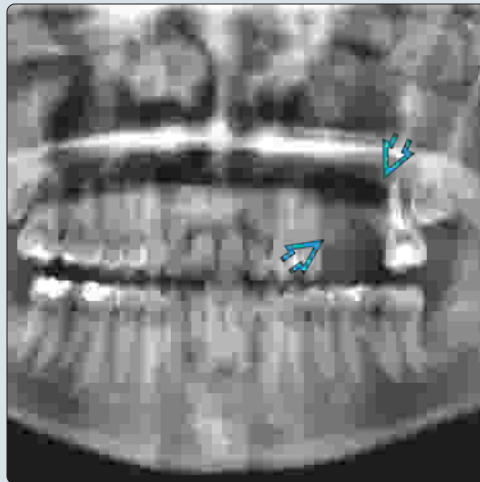
- Well-circumscribed, yellow-white cut surface
- Collagen stroma, dense to myxoid
- Odontogenic epithelium may or may not be present
- Cementum or dentin-like calcifications
- Dystrophic calcifications

TOP DIFFERENTIAL DIAGNOSES

- Dental follicle
- Desmoplastic fibroma, myxofibroma, fibrosarcoma

Radiolucent Cyst in Maxilla

(Left) This 20-year-old man presented to his dentist with mild pain in the upper left quadrant. Clinically there was a palatal bone impression overlying this large radiolucent lesion. (Right) Low-power view shows isolated epithelial islands and associated calcification in a dense fibrous stroma, a finding characteristic for odontogenic fibroma.

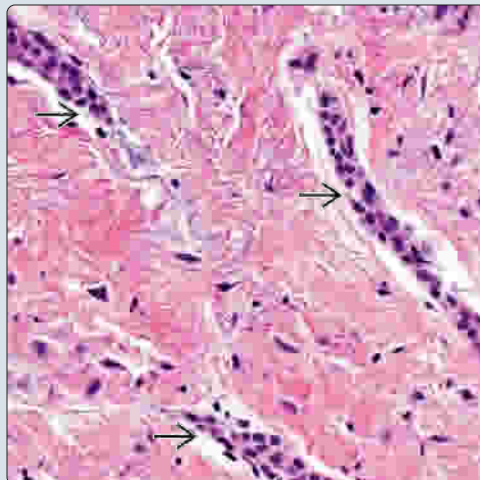


Calcifications and Epithelium in Stroma

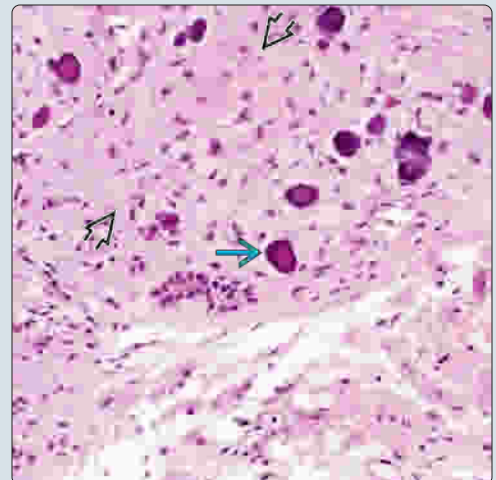


Cords of Odontogenic Epithelium

(Left) Cords of odontogenic epithelium are within fibrous stroma. Odontogenic epithelium is not always readily identified and is not required for diagnosis. However, the presence of odontogenic epithelium is reassuring and can often be identified by deeper or step sections. (Right) Medium-power image shows the rare granular cell variant of central odontogenic fibroma. Note the dystrophic calcifications that may result in radiopaque flecks on the associated radiographs.



Numerous Calcifications



TERMINOLOGY

Abbreviations

- Central odontogenic fibroma (COF)

Definitions

- Benign odontogenic neoplasm showing varying amounts of inactive-appearing odontogenic epithelium embedded in mature fibrous stroma

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Most are considered to be of periodontal ligament origin
- Dental follicle may be consideration
- Peripheral odontogenic fibroma is soft tissue counterpart

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon
- Age
 - Wide range; mean: 40 years
- Sex
 - Female > male (3:1)

Site

- Mandible: Usually posterior to 1st molar
- Maxilla: Usually anterior to 1st molar/premolar region

Presentation

- Asymptomatic
 - Detected on routine dental radiographs
- Symptomatic
 - Swelling, loosening of teeth, mild pain to painless, draining
 - Lesions of anterior maxilla
 - May have palatal bony depression
 - Occasionally creates characteristic cleft

Treatment

- Enucleation or curettage

Prognosis

- Excellent
 - Few recurrences
 - Appears to have limited growth potential
 - Especially in anterior maxilla

IMAGING

Radiographic Findings

- Unilocular, radiolucent
 - Usually small lesions
- Multilocular, radiolucent
- Frequently associated with unerupted tooth
- Expansion of affected bone
- Root resorption, sometimes subtle
- Root divergence of associated teeth
- Occasional radiopaque flecks
- Sclerotic, well-defined border

MACROSCOPIC

General Features

- Well circumscribed; firm, yellow-white, cut surface

Size

- Variable, but usually < 3 cm

MICROSCOPIC

Histologic Features

- Simple type
 - Fibroblasts within stroma
 - Collagen stroma, dense to myxoid
 - Odontogenic epithelium may or may not be present
 - Cementum or dentin-like calcifications
 - Dystrophic calcifications
 - Focal inflammation
- WHO (World Health Organization) type
 - Subclassification term that is being phased out
 - Complex pattern of cellular fibrous tissue, dense to myxoid
 - Long cords or larger nests of odontogenic epithelium predominate
 - Dystrophic calcifications
 - Cementum or dentin-like calcifications
 - Focal inflammation
- Granular cell type
 - Rare, composed of large, round granular cells

DIFFERENTIAL DIAGNOSIS

Dental Follicular Tissue

- Always associated with unerupted tooth
- Usually stroma is myxoid

Desmoplastic Fibroma

- More aggressive presentation
- Lacks odontogenic epithelial rests

Myxofibroma

- More acellular and myxoid
- Odontogenic epithelial rests rare

Fibrosarcoma

- Cellular neoplasm with uniform spindle cells in fascicular pattern
- Usually numerous mitoses
- More aggressive clinical presentation

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KEY FACTS

TERMINOLOGY

- Neoplasm of cementum intimately involved with tooth root

CLINICAL ISSUES

- Favors mandible
 - Premolar-molar region
- Removal of affected tooth and mass
 - Recurrence is considered rare with complete removal
- < 6% of odontogenic tumors
- Most common in 2nd to 3rd decade
- Tooth may test vital or vitality testing may be equivocal
- Removal of affected tooth and mass or retention if prior root canal

IMAGING

- Intimately associated with tooth root (pathognomonic)
- Radiopaque mass
- Narrow radiolucent rim

MACROSCOPIC

- Yellow mineralized tissue
- Fused to root

MICROSCOPIC

- Dense cementum-like tissue
- Prominent basophilic reversal lines
- Plump cementoblasts may line trabeculae

TOP DIFFERENTIAL DIAGNOSES

- Osteoblastoma
- Osteoid osteoma
- Osteosarcoma
- Reactive lesions
 - Periapical cyst
 - Periapical granuloma

DIAGNOSTIC CHECKLIST

- Radiographic presentation is nearly pathognomonic

(Left) Radiograph shows a radiodensity intimately associated with the roots of a mandibular molar. The periphery of the mass is surrounded by a characteristic radiolucent rim. This lesion was treated with surgical removal of the affected tooth and its mass. **(Right)** Hematoxylin & eosin shows the intimate relationship of the tumor to the root of this mandibular molar. Generally the specimen will be submitted in fragments as a surgical extraction is required to remove the entire mass.

Large Cementoblastoma of Mandible

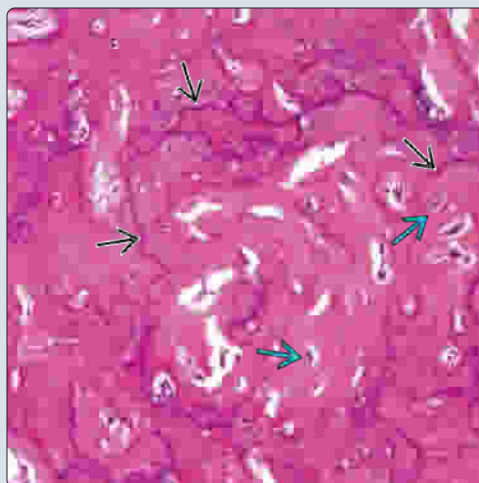


Fused Cementoblastoma to Tooth

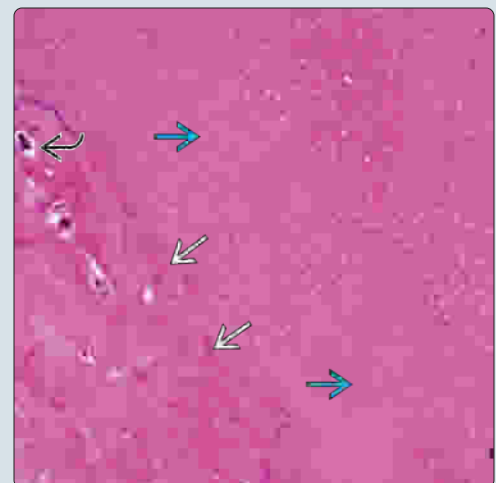


(Left) H&E shows the numerous, prominent, basophilic reversal lines. Irregular lacunae are also seen. **(Right)** H&E shows the mature tubular dentin in close association with the neoplastic cementum of a cementoblastoma. Note the irregular lacunae. Other entities in the differential diagnosis, like osteoblastoma and osteoid osteoma, do not have this intimate relationship with the tooth structure.

Basophilic Reversal Lines



Dentin Fused to Cementum



TERMINOLOGY**Synonyms**

- True cementoma
- Benign cementoblastoma

Definitions

- Neoplasm of cementum intimately involved with tooth root

CLINICAL ISSUES**Epidemiology**

- Incidence
 - < 6% of odontogenic tumors
- Age
 - Most common in 2nd to 3rd decade
- Sex
 - Probably equal gender distribution; series vary based on selection bias

Site

- Favors mandible; premolar-molar region
- Maxilla
- Always intimately associated with tooth root
 - Erupted permanent teeth
 - Rarely impacted teeth
 - Rarely deciduous teeth

Presentation

- Asymptomatic
- Symptomatic
 - Pain
 - Swelling
- Associated tooth
 - Tooth may test vital or vitality testing may be equivocal
- Rarely multiple

Treatment

- Surgical approaches
 - Removal of affected tooth and mass
- Alternate treatment
 - Retention of tooth with prior endodontic treatment (root canal)

Prognosis

- Recurrence is considered rare with complete removal
- Incomplete removal may result in recurrences, follow-up is indicated

IMAGING**Radiographic Findings**

- Radiopaque mass
- Narrow radiolucent rim
- Intimate association with tooth root (pathognomonic)
- Rare perforation of cortex
- Root resorption may be seen

MACROSCOPIC**General Features**

- Yellow mineralized tissue
- Fused to root

MICROSCOPIC**Histologic Features**

- Dense cementum-like tissue
 - Prominent basophilic reversal lines
 - Irregular lacunae
 - Plump cementoblasts may line trabeculae
 - Cellular fibroblastic tissue between mineralized trabeculae
- Periphery of lesion
 - Uncalcified matrix
- Occasional giant cells

DIFFERENTIAL DIAGNOSIS**Osteoblastoma**

- Does not have intimate relationship to tooth root
- Rare in jaw

Osteoid Osteoma

- Does not have intimate relationship to tooth root
- Rare in jaw
- Likely painful

Osteosarcoma

- Radiographically poorly circumscribed
- May demonstrate rapid growth
- Atypical histological proliferation

Reactive Lesions

- Periapical cyst
 - Almost always associated with non-vital tooth
 - Radiolucent lesion
 - Epithelial lining with inflammation
- Periapical granuloma
 - Almost always associated with non-vital tooth
 - Radiolucent lesion
 - Granulation type tissue reaction with inflammation

DIAGNOSTIC CHECKLIST**Clinically Relevant Pathologic Features**

- Radiographic presentation is nearly pathognomonic

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KEY FACTS

TERMINOLOGY

- Benign bone neoplasm with lamellar bone formation, osteoblastic rimming, and connective tissue stroma
 - Cemento-ossifying fibroma (COF)
 - When cementum is present, term COF is used
 - Juvenile ossifying fibroma (JOF)

CLINICAL ISSUES

- Age
 - COF: Peak in 3rd-4th decades
 - JOF: Peak in 2nd decade
- Sex
 - COF: Female >> male (5:1)
 - JOF: Male = female
- Usually asymptomatic
- Site
 - COF: Mandible most commonly affected (up to 90%)
 - JOF: Maxilla > mandible

IMAGING

- Well-demarcated, expansile, monostotic mass with mixed soft tissue center surrounded by ossifying rim

MICROSCOPIC

- Evenly spaced spicules of woven bone
- Osteoblasts and osteoclasts surround spicules
- Prominent calcified structures
- Cellular stellate stroma
- Histologic variants include: COF, JOF



ANCILLARY TESTS

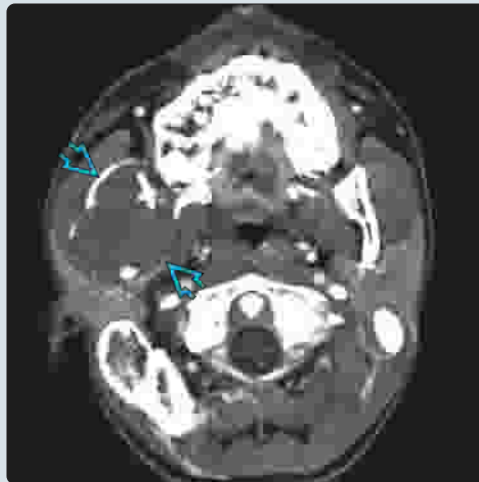
- *GNAS* gene mutations absent (characteristic of fibrous dysplasia)

TOP DIFFERENTIAL DIAGNOSES

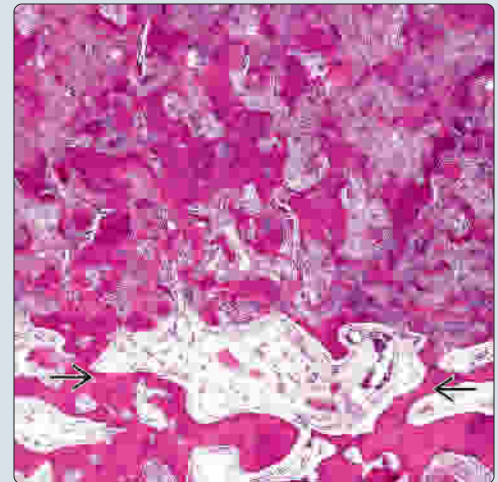
- Fibrous dysplasia
- Cemento-osseous dysplasia

CT of Right Mandible Ossifying Fibroma


(Left) CT scan (with contrast) shows a well-delimited, solitary radiolucent to focally radiopaque mass with a central area of low attenuation . Note the bony spicules at the periphery with irregular calcifications in the center. (Right) Uninvolved bone  is noted at the inferior aspect of the image. The stroma and numerous bony spicules and fragments are noted in the remaining sample. The cellularity of the stroma is quite distinctive compared to the stroma of the uninvolved bone.

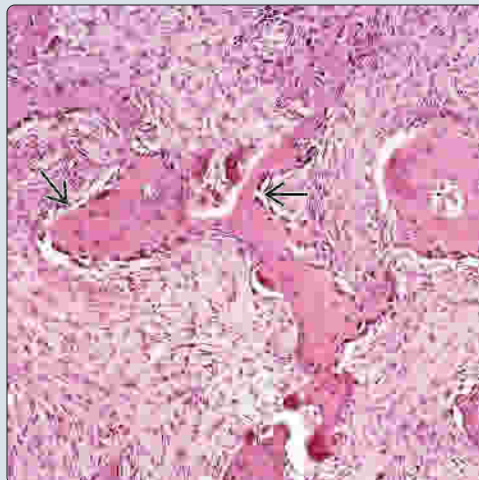


Low-Power Ossifying Fibroma

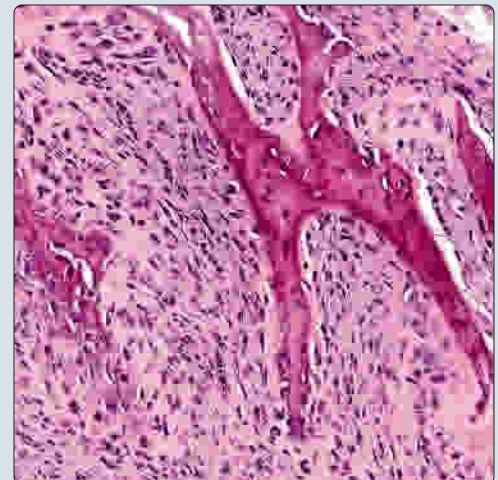


Osteoblastic Rimming

(Left) Spicules of bone in this ossifying fibroma show well-developed osteoblastic rimming . The stroma is cellular, but is not atypical. No giant cells or osteoclasts are seen in this field. (Right) There are evenly spaced spicules of woven bone separated by a spindle cell proliferation. Note the focal osteoblastic rimming around the spicules of bone. Osteoclasts can be present.



Cellular Stroma in Ossifying Fibroma



TERMINOLOGY

Abbreviations

- Ossifying Fibroma (OF)
- Cemento-ossifying fibroma (COF)
- Juvenile ossifying fibroma (JOF)

Definitions

- Benign neoplasm of bone with lamellar bone formation, osteoblastic rimming, and connective tissue stroma

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare
- Age
 - COF: Peak in 3rd-4th decades
 - JOF: Peak in 2nd decade
- Sex
 - COF: Female >> male (5:1)
 - JOF: Male = female

Site

- COF: Mandible most commonly affected (up to 90%)
 - Posterior, premolar regions specifically
- JOF: Maxilla > mandible

Presentation

- Vast majority are asymptomatic, identified by routine radiographic studies
- Slow growing but can have rapid increase in size

Treatment

- Options, risks, complications
 - Small lesions can be managed with watchful waiting
- Surgical approaches
 - Complete removal to avoid recurrence
- Radiation
 - Radiotherapy contraindicated, as it may induce malignant transformation

Prognosis

- Prognosis is excellent
- Recurrences develop if incompletely excised

IMAGING

Radiographic Findings

- Well-demarcated, expansile, unilocular monostotic mass with mixed soft tissue center surrounded by ossifying rim
- May cause teeth displacement, root divergence

CT Findings

- Sharply demarcated, expansile, mixed soft tissue and bone density lesion

MACROSCOPIC

General Features

- Well circumscribed, with definite boundaries
- Tumor "shelling out" is common
- Cut surface: Tan-white, dry, avascular, smooth mass

Size

- Range: 0.5-10 cm
 - Largest lesions tend to be mandibular

MICROSCOPIC

Histologic Features

- Composed of variable amounts of fibrous tissue proliferation and calcifications
- Evenly spaced spicules of woven bone
 - Lamellar transformation at periphery
 - Coalesce to form curvilinear trabeculae (often acellular)
 - Osteoblasts and osteoclasts surround spicules
 - Osteoblastic rimming is prominent
- Prominent calcified structures (ossicles, cementicles)
 - Eosinophilic or basophilic spherules of cementum-like tissue
- Cellular, fibroblastic spindled cell stroma with sparse collagen
- Multinucleated giant cells or osteoclasts may be seen
- Mitoses are inconspicuous
- Histologic variants include
 - COF (odontogenic origin)
 - JOF
 - Psammomatoid type
 - Highly cellular stroma, mitoses, psammomatous calcifications

ANCILLARY TESTS

Genetic Testing

- Mutations in *HRPT2* gene reported
- *GNAS* gene mutations absent
- *MDM2* gene amplification in JOF

DIFFERENTIAL DIAGNOSIS

Fibrous Dysplasia

- Radiographic separation is difficult
- Irregularly shaped trabeculae of immature woven bone without osteoblastic rimming

Cemento-Osseous Dysplasia

- Sclerotic radiodensity, lacking osteoblastic rimming

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KEY FACTS

TERMINOLOGY

- Psammomatoid juvenile ossifying fibroma (PJOF)
- Trabecular juvenile ossifying fibroma (TJOF)
- Benign fibroosseous neoplasm composed of mixture of stroma and bone characterized by rapid growth

CLINICAL ISSUES

- **PJOF:** Age range: 3 months to 72 years; mean: 16-33 years
 - Paranasal sinuses (~ 90%): Ethmoid > frontal > maxillary > sphenoid > temporal bone
- **TJOF:** Age range: 8.5-12 years
 - Maxilla > mandible
- Excellent prognosis after complete excision, with increased recurrence rate (30-58%) if incompletely resected

IMAGING

- **TJOF:** Well-demarcated, mixed soft tissue density, unilocular with central area surrounded by ossified rim (eggshell periphery)

MICROSCOPIC


- Unencapsulated with infiltration into adjacent bone
- Hypercellular stroma of small uniform stellate and spindle-shaped fibroblast-like cells with scant collagen
- **PJOF:** Numerous small, rounded, mineralized collagenous ossicles and immature osteoid
 - Cystic degeneration and aneurysmal bone cyst formation
- **TJOF:** Osteoid develops from fibrous stroma as long, slender strands (paint brush strokes)

ANCILLARY TESTS

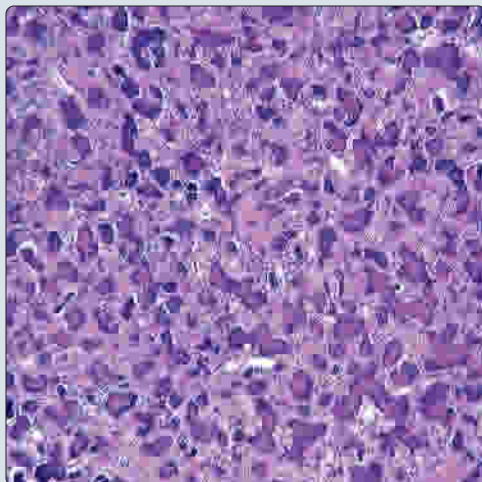
- **MDM2** amplification in up to 70% (~ 33% in ossifying fibroma) **without** IHC MDM2 overexpression

TOP DIFFERENTIAL DIAGNOSES

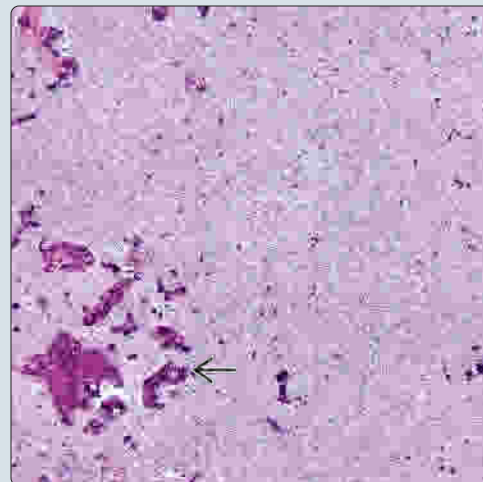
- Fibrous dysplasia, cementoblastoma, meningioma, osteoma, osteosarcoma

(Left) This psammomatoid juvenile ossifying fibroma (PJOF) shows innumerable small, rounded, mineralized collagenous ossicles that are psammomatous bodies. Partial fusion is noted. **(Right)** There is a very cellular stroma arranged in a nondescript fashion of uniform stellate and spindled-shaped fibroblasts. Isolated calcifications and psammomatous bodies are noted .

Innumerable Psammomatous Bodies

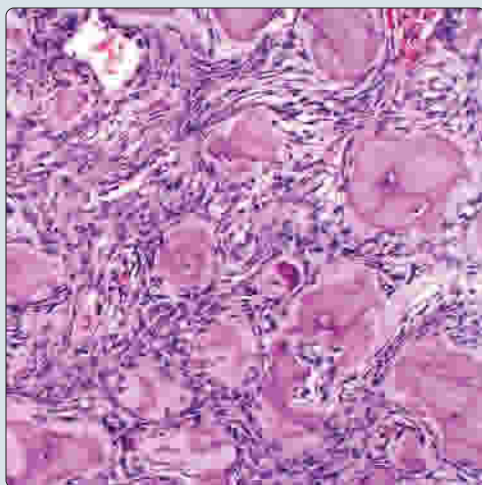


Hypercellular Stroma With Calcifications

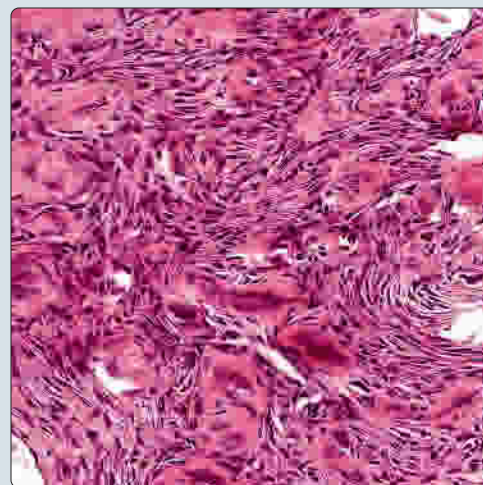


(Left) The ossicles or cementicles show varying degrees of mineralization. The material appears bony. They seem to arise straight out of the cellular stroma without osteoblastic rimming. **(Right)** There is a spindled cellular stroma lacking any pleomorphism. The calcifications show a heavy collagenized collar around the calcifications. Psammoma-like bodies are not identified in this field.

Ossicles With Fibrous Stroma



Irregular Calcifications



TERMINOLOGY

Abbreviations

- Juvenile active ossifying fibroma (JAOF)
- Psammomatoid juvenile ossifying fibroma (PJOF)
- Trabecular juvenile ossifying fibroma (TJOF)

Synonyms

- Aggressive psammomatoid ossifying fibroma (OF)

Definitions

- Benign fibroosseous neoplasm composed of mixture of stroma and bone characterized by rapid growth

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare, much less common than conventional OF
- Age
 - **PJOF**: Range: 3 months to 72 years; mean: 16-33 years
 - **TJOF**: Range: 8.5-12 years
- Sex
 - Equal gender distribution

Site

- **PJOF**: Paranasal sinuses (~ 90%): Ethmoid > frontal > maxillary > sphenoid > temporal bone
- **TJOF**: Maxilla > mandible

Presentation

- Progressive to rapid expansion of affected bone(s)
 - May be due to hemorrhage or aneurysmal bone cyst formation
- Chronic sinusitis, obstruction, pain, epistaxis
- Proptosis, exophthalmos, diplopia, or visual acuity loss

Treatment

- Surgical approaches
 - Total removal, avoiding radical resection procedures

Prognosis

- Excellent prognosis after complete excision
- Increased recurrence rate (30-58%) if incompletely resected for sinus > gnathic tumors

IMAGING

Radiographic Findings

- Bone algorithm CT studies are best
- **TJOF**: Well-demarcated, mixed soft tissue density, unilocular with central area surrounded by ossified rim (eggshell periphery)
- **PJOF**: Well-defined, round, often multiloculated, osteolytic lesion with sclerotic and low-density areas, dependent on calcification or cystic change

MACROSCOPIC

General Features

- Well-demarcated but unencapsulated, with tendency to infiltrate adjacent bone
- Cut surface: Yellowish-white with firm to gritty consistency

Size

- Range: 0.5-10 cm

MICROSCOPIC

Histologic Features

- Unencapsulated with infiltration into adjacent bone
- Composed of variable amounts of fibrous tissue proliferation and calcifications
- Hypercellular stroma of small uniform stellate and spindle-shaped fibroblast-like cells with scant collagen
- Multinucleated giant cells and scattered mitotic figures

Psammomatoid Juvenile Ossifying Fibroma

- Numerous small, rounded, mineralized collagenous ossicles and immature osteoid
 - Collagenous chondrilles, cementum-like psammomatous bodies (cementicles): Deeply basophilic
 - Curved bodies with thick, irregular collagenous rim
 - Ossicles may fuse to form larger bone trabeculae
- Cystic degeneration and aneurysmal bone cyst formation

Trabecular Juvenile Ossifying Fibroma

- Osteoid develops from fibrous stroma as long, slender strands (paint brush strokes)
- Irregular central mineralization produces immature bone trabeculae **without** osteoblastic rimming

ANCILLARY TESTS

Genetic Testing

- Chromosome 12 long arm rearrangement covering *MDM2* and *RASAL1*
- *MDM2* amplification in up to 70% (~ 33% in OF) **without** IHC MDM2 overexpression

DIFFERENTIAL DIAGNOSIS

Fibrous Dysplasia

- Radiographic separation is difficult with poorly defined expansion, classic ground-glass appearance, mixed patterns
- Most are monostotic (70%), but when polyostotic, helps to exclude JAOF

Cementoblastoma

- Dense mass associated with tooth root, arising from periodontal ligament region
- Cementicles can mimic calcifications or cementicle-like deposits in JAOF

Meningioma

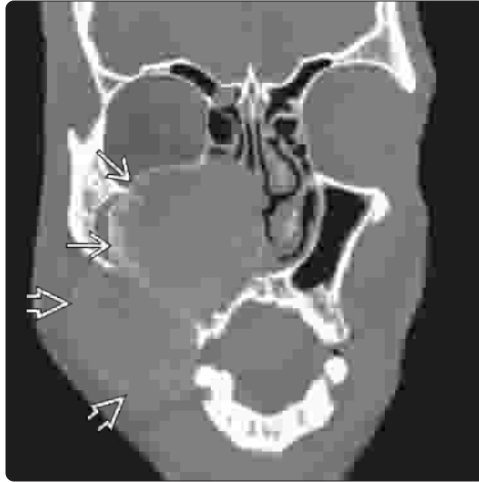
- Epithelial appearance arranged in whorled architecture with psammoma bodies

SELECTED REFERENCES

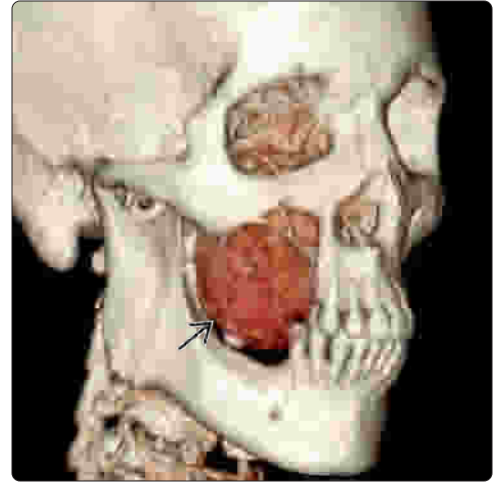
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(Left) Coronal bone CT best delineates this bilobed morphology with the intrasinus component demonstrating the peripheral ossification [X], a finding not present in the extrasinus portion [X]. This erosion and extension results in clinical manifestations, which may be many. (Right) CT reformat highlights the extrasinus portion of the lesion [X], as it has expanded into the adjacent soft tissues. There is usually a very thin, eggshell appearance at the periphery.

CT of Maxillary Sinus and Soft Tissue Mass



Reconstructed CT of Maxillary Mass

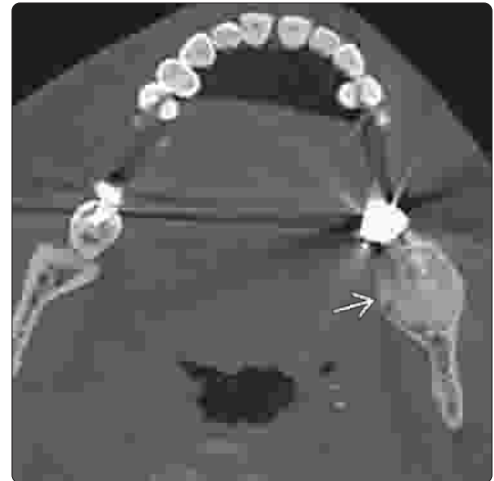


(Left) Axial T2WI MR demonstrates a well-defined mass [X] within the frontal sinus, showing a very hyperintense signal. Fibrous areas are hyperintense (usually center and cystic areas), while ossified areas are usually hypointense. (Right) There is a well-defined mixed radiolucent and radiopaque solitary lesion affecting the ramus of the mandible [X]. This well-demarcated appearance is characteristic of a trabecular juvenile ossifying fibroma.

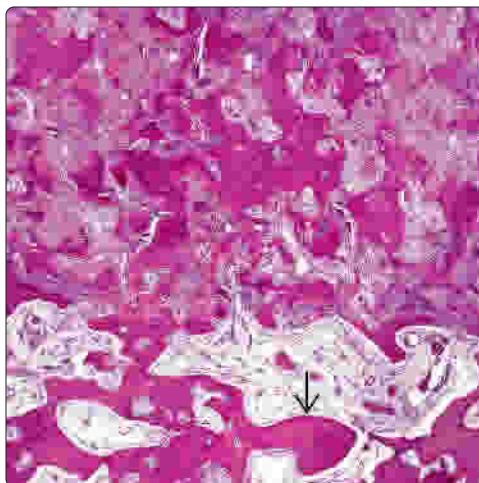
MR With Hyperintense Frontal Sinus Mass



CT of Mandible Trabecular Juvenile Ossifying Fibroma

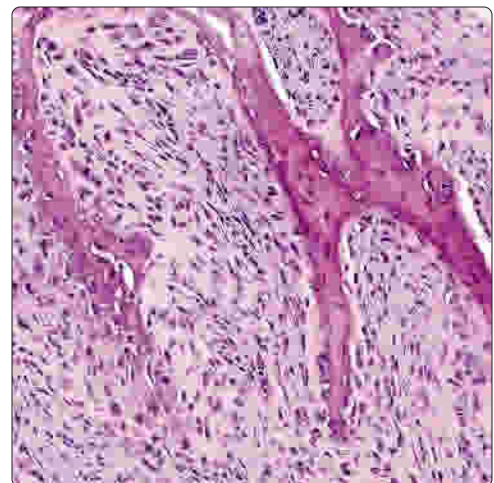


Trabecular Juvenile Ossifying Fibroma With Large Bony Trabeculae

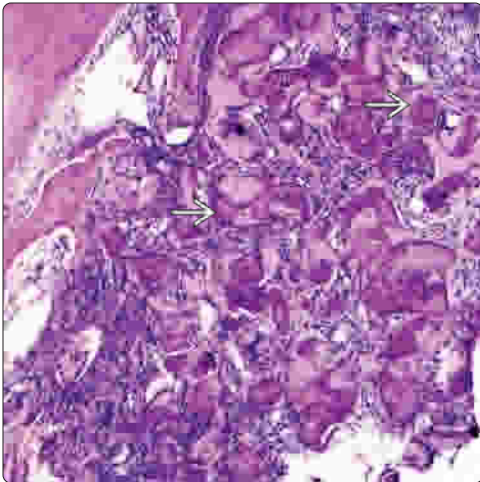


(Left) There is separation from the adjacent bone [X] with large trabeculae of bony tissue set within a cellular fibrous stroma. There is no osteoblastic rimming. (Right) Long, slender strands of osteoid within a fibrous stroma are shown. There is early mineralization. Osteoblastic rimming is inconspicuous in this lesion.

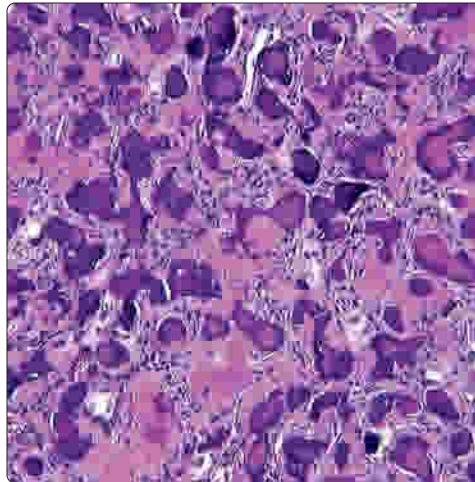
Trabecular Juvenile Ossifying Fibroma With Elongated Bony Trabeculae



Cementicles Within Psammomatoid Juvenile Ossifying Fibroma

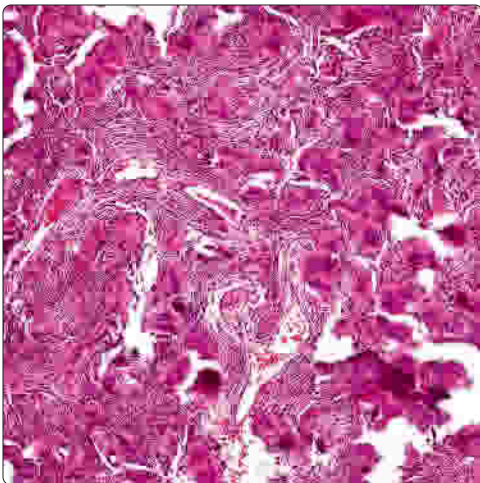


Basophilic Calcifications

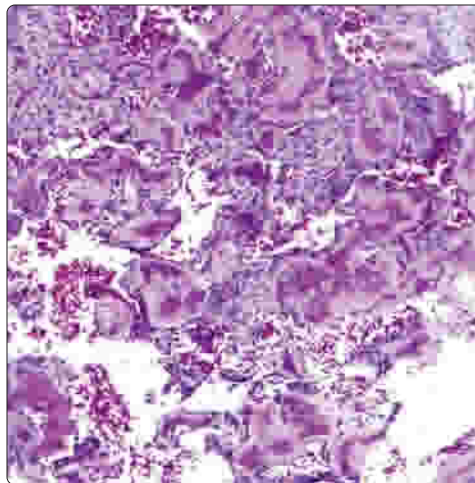


(Left) Lesions display cementicles that resemble true psammoma bodies. The background spindle cells are bland and without mitotic figures. Vessels are present but are thin and delicate. **(Right)** A cellular stroma is filled with small, rounded to curved, mineralized collagenous ossicles. The collagenous rim is thick and irregular. The ossicles are focally fused.

Irregular Mineralization of Chondriles

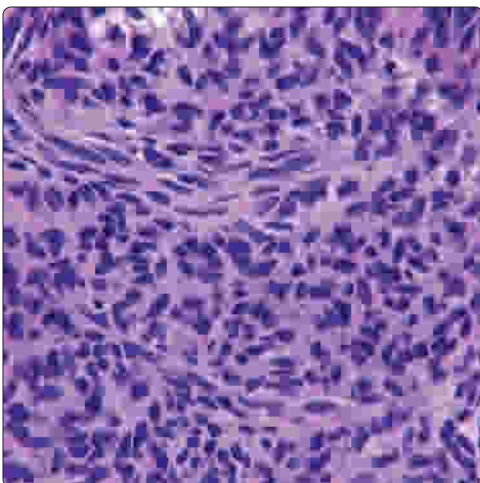


Irregular Shapes

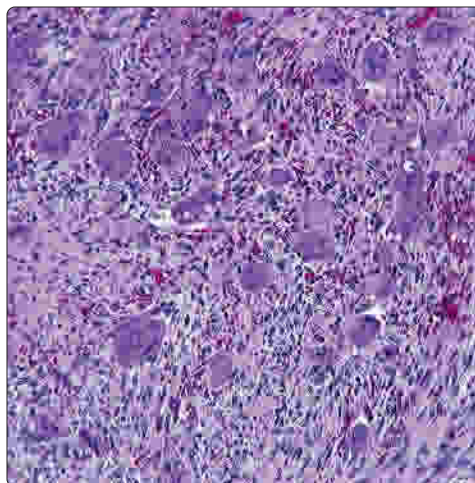


(Left) There is a prominent collagenous rim at the edge of each psammomatous body without any well-developed osteoblastic rimming. The ossicles are set within a very well-developed cellular stroma. **(Right)** The ossicles or psammomatous bodies may fuse into irregular bony trabeculae, but are still associated with the fibrous connective tissue stroma.

Hypercellular Stroma



Multinucleated Giant Cells With Blood



(Left) H&E shows hypercellular stroma of small uniform stellate and spindle-shaped fibroblast-like cells with scant collagen formation. There are no mineralized bodies in this field. **(Right)** Multinucleated giant cells with areas of hemorrhage can be seen in association with juvenile active ossifying fibroma. This may be referred to as an aneurysmal bone cyst-like formation, a finding seen in larger lesions.

KEY FACTS

TERMINOLOGY

- Benign surface osteogenic lesion characterized by proliferation of compact or cancellous cortical bone
- Separated based on specific location

CLINICAL ISSUES

- Peak during 2nd to 6th decades
- May be single or multiple
- Most common in craniofacial bones, as follows
 - **Nasal:** Nasal and paranasal sinuses and bones (2-3%)
 - **External auditory canal (EAC)** most common
 - **Temporal bone and skull (4-5%)**
 - **Jaw:** Mandible and palate most frequently affected
- Slow-growing lesions, usually asymptomatic, incidental findings on imaging studies
- Clinical signs and symptoms depend on location, size, and growth direction

IMAGING

- Small, uniformly radiodense, sharply marginated mass
- Broad base of attachment to underlying cortex, merging imperceptibly

MACROSCOPIC

- Very dense, hard, cortical bone, with smooth surface

MICROSCOPIC

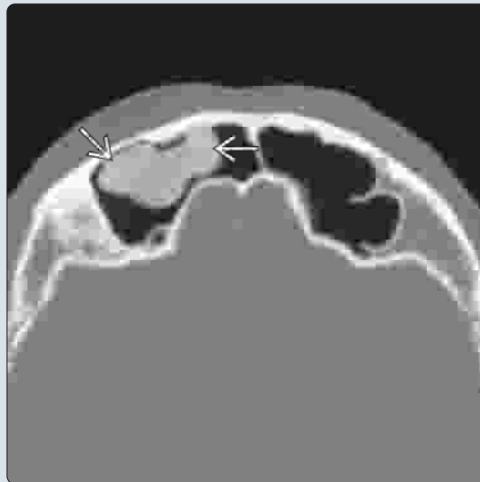
- Dense lamellae with organized haversian canals
- Peripheral area of compact bone
- Underlying cancellous bone with networks of trabeculae within fibrovascular stroma
- Central portion of loose fibrous stroma containing blood vessels and plump osteoblasts

TOP DIFFERENTIAL DIAGNOSES

- Osteochondroma, chondroma, exostoses

CT of Frontal Sinus Osteoma

(Left) Axial CT image demonstrates a well-defined mass in the right frontal sinus. The lesion is located well above the frontal sinus drainage pathway and no obstructed secretions are identified. **(Right)** The surface squamous epithelium is uninvolved by the osteoma. There is a very well-formed, mature compact bony lesion in the stroma. This lesion expanded from the adjacent cortex, creating a bulging lesion in the oral cavity clinically.



Compact Bone of Osteoma

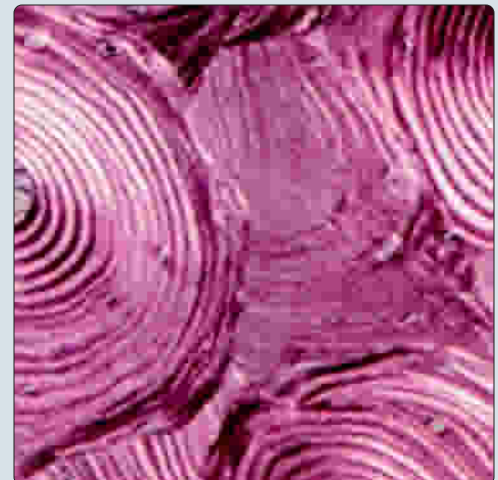


Compact Bone With Haversian System

(Left) This osteoma shows haversian bone with a delicate stroma within the interstices of bone. The surface epithelium is uninvolved. **(Right)** Polarized light demonstrates both the haversian-like arrangement of concentric rings of collagen layers, similar to a tree trunk seen in cross section.



Polarized Light Showing Concentric Rings



TERMINOLOGY**Synonyms**

- Cancellous osteomas: Osteoma spongiosum
- Compact osteomas: Osteoma durum

Definitions

- Osteoma is benign surface osteogenic lesion characterized by proliferation of compact or cancellous cortical bone
 - Also referred to as ivory or button osteoma

ETIOLOGY/PATHOGENESIS**Pathogenesis**

- Either true neoplasm or developmental anomaly

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Uncommon
- Age
 - Peak during 2nd to 6th decades
- Sex
 - Equal gender distribution
 - Nasal osteomas show slight male predominance

Site

- May be single or multiple
- Most common in craniofacial bones, as follows
 - **Nasal:** Nasal and paranasal sinuses and bones (2-3%)
 - Frontal > ethmoid > maxillary > sphenoid
 - **External auditory canal:** Most common ear site
 - **Temporal bone and skull (4-5%)**
 - **Jaw:** Mandible and palate most frequently affected
 - Torus palatini and mandibularis are terms used in this site

Presentation

- Slow-growing lesions, usually asymptomatic, incidental findings on imaging studies
- Clinical signs and symptoms depend on location, size, and growth direction
- Conductive hearing loss due to ossicular chain impingement
- Eustachian tube obstruction may cause otitis media with effusion
- Sinus ostium obstruction: Facial pain, nasal obstruction, sinusitis, or mucocele
- Nasolacrimal duct compression may cause epiphora
- Gardner syndrome (autosomal dominant inheritance)
 - Includes multiple osteomas, polyposis of large bowel, epidermoid or sebaceous cysts, cutaneous fibromas
 - Should be considered with multiple osteomas or presentation at young age

Treatment

- Asymptomatic osteomas can be followed with periodic radiographic evaluation
- Surgery (endoscopic) for symptomatic lesions, depending on patient symptoms, tumor location and size

IMAGING**Radiographic Findings**

- Usually incidental finding on imaging
- Small (usually < 2 cm) uniformly radiodense sharply marginated mass
- Broad base of attachment to underlying cortex, merging imperceptibly

MACROSCOPIC**General Features**

- Very dense, hard, cortical bone, with smooth surface

MICROSCOPIC**Histologic Features**

- Dense lamellae with organized haversian canals
- Varying degrees of 3 tissue types
 - Peripheral area of compact bone
 - Underlying cancellous bone with networks of trabeculae within fibrovascular stroma
 - Central portion of loose fibrous stroma containing blood vessels and plump osteoblasts
 - Osteoblasts rimming bone are inconspicuous, small, and attenuated
- Intratrabecular stroma contains
 - Osteoblasts, fibroblasts, giant cells
 - Variable osteoblastic and osteoclastic activity, but usually limited
 - No hematopoietic cells
- Many fibrovascular channels surrounded by lamellar bone
- 3 histologic types of osteoma are described
 - Compact, spongiotic, mixed

DIFFERENTIAL DIAGNOSIS**Osteochondroma**

- **Radiology:** Pedunculated or sessile lesion on bony stalk
 - Cartilage cap ± mineralization
- **Pathology:** Endochondral ossification similar to growth plate
 - Bony stalk with overlying cartilage cap

Chondroma

- **Radiology:** Lobular organization and calcification
- **Pathology:** Lobules of hyaline-type cartilage only

Exostoses

- **Radiology:** No underlying connection with marrow cavity
- **Pathology:** Bony stalk with overlying cartilage cap

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KEY FACTS

TERMINOLOGY

- Benign, bone-forming neoplasm producing woven bone spicules bordered by prominent osteoblasts

CLINICAL ISSUES

- ~ 90% of cases within first 2 decades; mean: 23 years
- Predilection for posterior mandible (> 70%)
- Clinical manifestations depend on site and size of lesion: Pain, swelling, tenderness
- Local conservative excision and thorough curettage

IMAGING

- May appear radiolucent or semiradiolucent with radiopaque mottling
- Well-demarcated, narrow, radiolucent margin
- Cortical erosion/expansion/perforation is generally surrounded by thin shell of new bone

MACROSCOPIC

- Yellow to red, gritty or sandpaper-like due to

- Mineralization, often cystic with blood-filled spaces

MICROSCOPIC

- Characterized by mixture of bone spicules, osteoblasts, and vascularized stroma
- Islands of haphazardly arranged wide, irregular bony spicules undergoing varying degrees of calcification
 - Does **not** permeate preexisting bone
- Abundant, plump epithelioid osteoblasts surrounding bony trabeculae or forms sheets
- Well-vascularized stroma with numerous multinucleated cells adjacent to bone

TOP DIFFERENTIAL DIAGNOSES

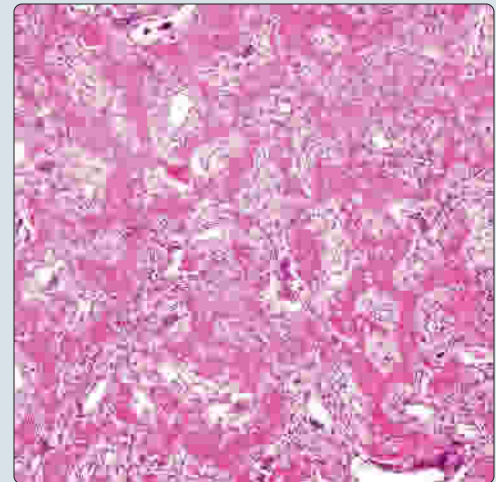
- Osteosarcoma, fibrous dysplasia, osteoid osteoma, Paget disease, central giant cell lesion
- Ossifying fibroma, chondroblastoma, cementoblastoma, odontogenic fibroma, cementoosseous dysplasia

Large Radiolucent Mandible Mass

(Left) A large mandibular lesion appears as a radiolucent mass with radiopaque mottling. There is a well-demarcated, narrow, radiolucent margin. Note the expanded bone with a thin shell of new bone. **(Right)** Islands of haphazardly arranged spicules of bone show plump osteoblasts and a number of multinucleated cells adjacent to the bone trabeculae. The stroma is slightly cellular.

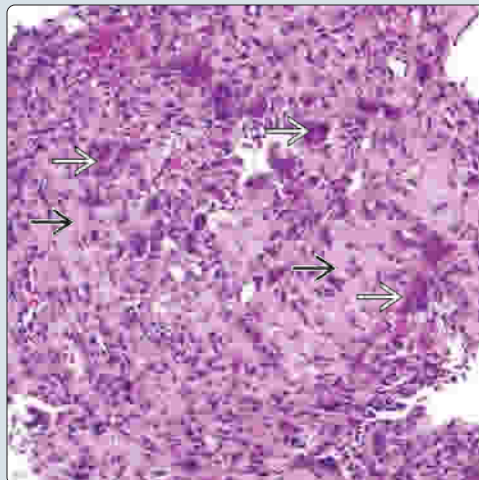


Spicules of Bone With Plump Osteoblasts

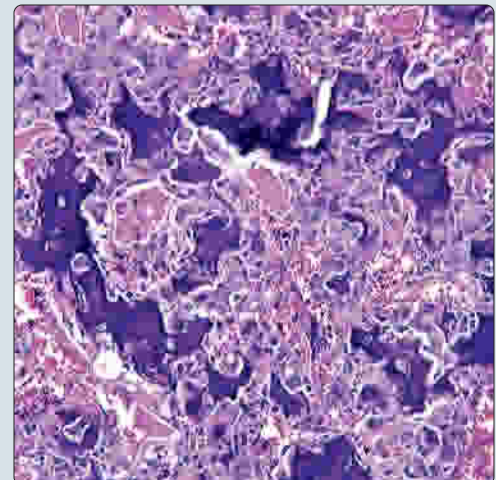


Osteoid Islands With Giant Cells

(Left) Islands and delicate fibrils of osteoid and abundant giant cells characterize osteoblastoma. Background spindle cells are bland with plump nuclei. **(Right)** This high-power view shows numerous osteoblasts adjacent to the bony spicules as well as within the stroma. They show prominent nucleoli and a plasmacytoid appearance.



Remarkably Plump Osteoblasts



TERMINOLOGY**Definitions**

- Benign, bone-forming neoplasm producing woven bone spicules bordered by prominent osteoblasts

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Rare, accounting for < 1% of all maxillofacial tumors
- Age
 - ~ 90% of cases within first 2 decades; mean: 23 years
- Sex
 - Female > male (1.1:1)

Site

- < 10% of osteoblastomas develop in jaws and skull
 - Predilection for posterior mandible (> 70%)
 - Mandible > maxilla
 - Intimately associated with tooth root

Presentation

- Clinical manifestations depend on site and size of lesion, characterized by pain, swelling, tenderness

Treatment

- Local conservative excision and thorough curettage usually adequate

Prognosis

- Benign behavior for vast majority
 - More aggressive if > 4 cm, multifocal and if anatomic confines limit resection
- Recurrences in ~ 8% of incompletely excised tumors
 - Usually develop within 1 year of initial surgery
- Metastasis does not develop

IMAGING**Radiographic Findings**

- Variable radiographic appearance
 - Depends on degree of calcification
 - Younger lesions may appear more radiolucent but ossify with maturation
 - May appear radiolucent or semiradiolucent with radiopaque mottling
 - Well-demarcated, narrow, radiolucent margin, but may expand bone
 - Cortical erosion and expansion/perforation is generally surrounded by thin shell of new bone

MACROSCOPIC**General Features**

- Yellow to red, gritty or sandpaper-like due to mineralization, often cystic with blood-filled spaces

Size

- Range: 2-10 cm
- Must be > 2 cm to distinguish from osteoid osteoma

MICROSCOPIC**Histologic Features**

- Characterized by mixture of bone spicules, osteoblasts, and vascularized stroma
- Islands of haphazardly arranged wide, irregular bony spicules undergoing varying degrees of calcification
 - Does **not** permeate preexisting bone
 - Prominent basophilic reversal lines
 - Lace-like osteoid deposition
- Abundant, plump epithelioid osteoblasts surrounding bony trabeculae or forms sheets
- Well-vascularized stroma with numerous multinucleated cells adjacent to bone
- Scant chronic inflammatory cells adjacent to vessels
- Absence of atypical mitoses and pleomorphism

ANCILLARY TESTS**Genetic Testing**

- t(1;2;14)(q42;q13;q24); abnormalities in chromosomes 1 and 14; recurrent 22q deletions

DIFFERENTIAL DIAGNOSIS**Osteosarcoma**

- Ill-defined mass with destructive borders, bone incorporation, cortical breakthrough and soft tissue extension
- Pleomorphism, malignant osteoid, atypical mitoses, necrosis

Fibrous Dysplasia

- Poorly defined radiographically, multilocular radiolucency, with ground-glass appearance
- Immature and woven bone, in an "alphabet letter" distribution
- Spindled cell stroma more dense, with less vascularity than osteoblastoma

Cementoblastoma

- Intimately fused to teeth roots; cementum-like material

Ossifying Fibroma

- More fibrous, less vascular, lacks large number of osteoblasts

Paget Disease

- Affects entire bone with mixed lucent/sclerotic areas
- Islands of bone; extensive remodeling and reversal lines, large osteoclasts, osteoblasts; increased vascularity without spindle cell stroma

Chondroblastoma

- Rare in jaw; chondrocytes with cartilaginous matrix; no osteoblastic activity

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3. Berry M et al: Osteoblastoma: a 30-year study of 99 cases. J Surg Oncol. 98(3):179-83, 2008

KEY FACTS

TERMINOLOGY

- Rare, biphasic, neuroblastic, and pigmented epithelial neoplasm of craniofacial sites

CLINICAL ISSUES

- 95% of patients < 1 year; 80% < 6 months
- Female > male (2:1)
- Maxilla (70%); mandible and skull (10% each)
- Rapidly growing mass with tooth displacement
- Even though rapidly growing and destructive, tends to have benign clinical course
- Recurrences are frequent (approximately 1/3)

IMAGING

- Intrabony expansive areas of radiolucency, usually with poorly demarcated margins

MACROSCOPIC

- Smooth, hard, firm mass, with mottled white-gray to blue-black cut surfaces

MICROSCOPIC

- Biphasic population
 - Centrally located, small, darkly staining cells
 - Larger, epithelioid, polygonal, melanin, pigmented cells
- Heavy, dense sclerotic stroma




ANCILLARY TESTS

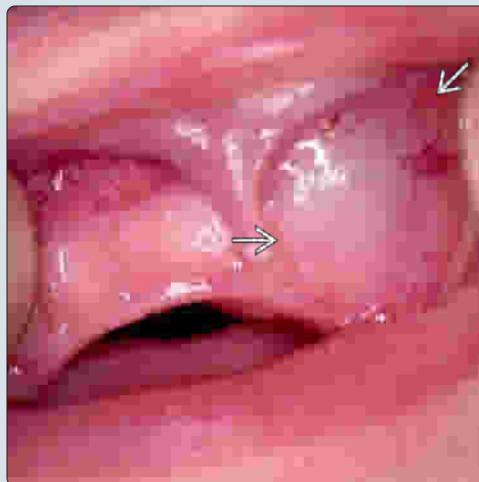
- Polyphenotype: Neural, melanocytic, epithelial
 - Large cells: Keratin, vimentin, HMB-45, NSE, CD57
 - Small cells: Synaptophysin, GFAP, NSE, CD57

TOP DIFFERENTIAL DIAGNOSES

- Rhabdomyosarcoma
- Ewing/PNET
- Lymphoma
- Melanoma

Blue Gingival Mass in Infant





(Left) Clinical photograph shows a bluish swelling of the gum  in an infant with an MNTI of the left maxilla. (Right) Gross photograph shows a dark, blue-black pigmented mass  associated with an area of cystic change . This tumor is from the maxilla.

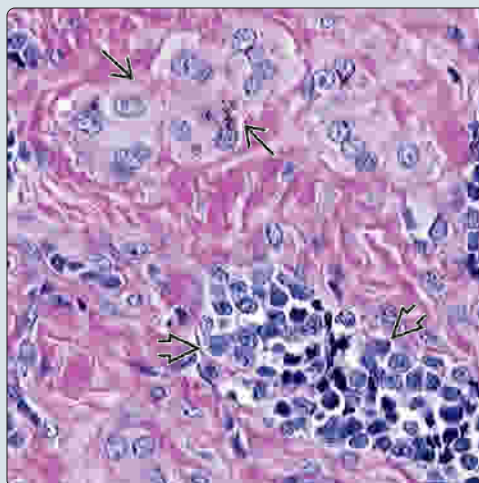


Dark Pigmentation Visible in Gross Sample

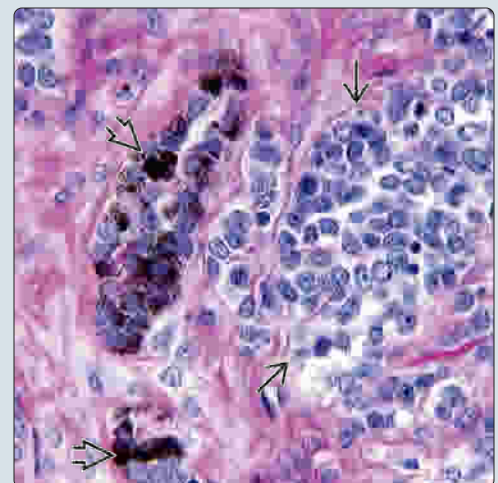


Biphasic Appearance With Pigmented Cells

(Left) Hematoxylin and eosin shows a biphasic population with heavy desmoplastic stroma separating the tumor islands. The large, epithelioid cells contain pigment . Nests of small round blue cells lack pigment . (Right) The neural-type cells have a very high nuclear to cytoplasmic ratio and delicate nuclear chromatin . The larger cells are nearly obscured by cytoplasmic heavy, granular melanin pigment .



Immature Cells in MNTI



TERMINOLOGY

Abbreviations

- Melanotic neuroectodermal tumor of infancy (MNTI)

Synonyms

- Melanotic progonoma

Definitions

- Rare, biphasic, neuroblastic, and pigmented epithelial neoplasm of craniofacial sites

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Congenital presentation
- Neural crest origin
 - Expression of melanotransferrin (melanoma-specific peptide that may play role in iron metabolism)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare; < 500 reported cases
- Age
 - 95% of patients < 1 year; 80% < 6 months
- Sex
 - Female > male (2:1)

Site

- Maxilla (70%); mandible and skull (10% each)

Presentation

- Rapidly growing mass with tooth displacement
 - Gives bluish appearance (pigment appears blue through mucosa)
- Usually maxillary anterior alveolar ridge

Laboratory Tests

- Elevated vanilmandelic acid levels

Treatment

- Even though rapidly growing and destructive, tends to have benign clinical course
- Complete local excision (usually by partial maxillectomy) with clear margins
- Chemotherapy for recurrent or residual tumors

Prognosis

- Good, but capricious, as no clinical or pathologic features predict behavior
- Recurrences are frequent (approximately 1/3)
- Metastases in < 10%: Lymph nodes, liver, bone, adrenal glands, soft tissue

IMAGING

General Features

- Intrabony expansive areas of radiolucency, usually with poorly demarcated margins
- Extensive tumor calcification may be identified

MACROSCOPIC

General Features

- Smooth, hard, firm mass, with mottled white-gray to blue-black cut surfaces
- Size range: 1-10 cm; mean: 3.5 cm

MICROSCOPIC

Histologic Features

- Circumscribed but not encapsulated
- Cells are arranged in alveolar or tubular configurations
- Biphasic population
 - Centrally located, small, darkly staining cells comprise majority of cells
 - Neural quality with scant, fibrillar cytoplasm
 - Round nuclei with coarse and heavy nuclear chromatin
 - Larger, epithelioid polygonal cells with vesicular nuclei
 - Much greater amount of opaque cytoplasm filled with granular melanin pigment
- Heavy, dense sclerotic vascularized fibrous connective tissue stroma
- Mitotic figures are absent
- Lacks hemorrhage and necrosis

ANCILLARY TESTS

Immunohistochemistry

- Polyphenotype: Neural, melanocytic, epithelial
 - Large cells: Keratin, vimentin, HMB-45, NSE, CD57
 - Small cells: Synaptophysin, GFAP, NSE, CD57
- Variable expression of EMA and S100 protein

DIFFERENTIAL DIAGNOSIS

Rhabdomyosarcoma

- Usually older age at presentation, with strong muscle markers and unique translocations
- Rhabdomyoblastic differentiation can be seen in MNTI

Lymphoma

- Lacks biphasic appearance and pigment, with **positive** lymphoid markers

Ewing/PNET

- Sheet-like, nonpigmented small round blue cells, **positive** with FLI1, CD99, chromogranin, S100 protein
- Diagnostic t(11;22) *EWSR1/FLI1* gene fusion product

Melanoma

- Very rare in infants, with S100 protein and SOX10 reaction; **negative** epithelial markers

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3. Nelson BL et al: Melanotic neuroectodermal tumor of infancy. *Ear Nose Throat J.* 85(6):365, 2006
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KEY FACTS

TERMINOLOGY

- Odontogenic tumor that shows malignant histologic features within ameloblastoma

CLINICAL ISSUES

- Extremely rare
- Most develop in mandible
- Definitive management difficult to determine due to limited case reports
- Painful swelling or mass
- Often associated with recent rapid growth
- Many present with metastatic disease
- All require radical resection
- Generally poor prognosis

IMAGING

- Ill-defined or irregular radiolucent lesion
 - Multilocular or unilocular
- Cortical expansion, frequently with perforation

- May infiltrate into adjacent structures




MICROSCOPIC

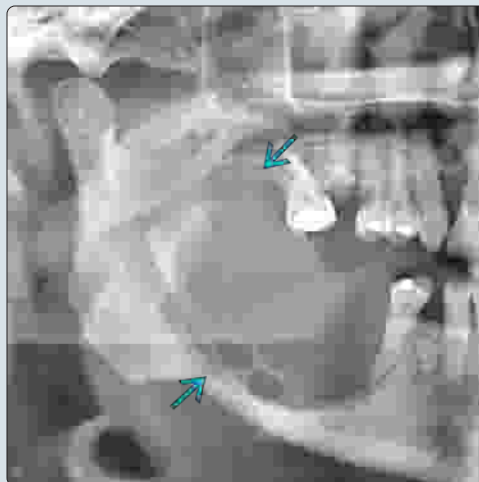
- Features of ameloblastoma
 - Peripheral palisading, reverse polarization, central stellate reticulum, any histologic subtype
- Epithelial atypia (carcinoma)
 - Profound pleomorphism with hyperchromasia, increased N:C ratio, loss of adhesion
- Mitoses are increased, including atypical forms
- Necrosis, vascular and perineural invasion

TOP DIFFERENTIAL DIAGNOSES

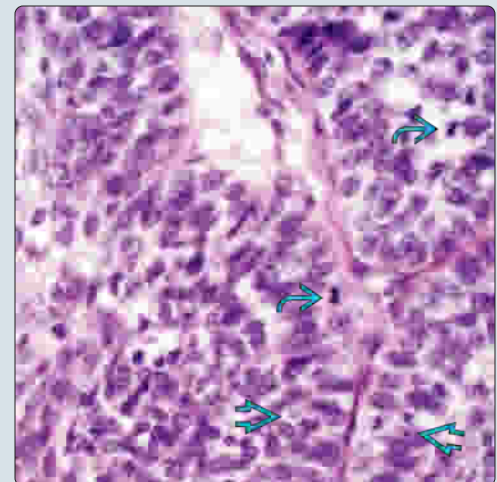
- Ameloblastoma
- Intraosseous squamous cell carcinoma
- Clear cell odontogenic carcinoma
- Metastatic disease

Mandibular Ameloblastic Carcinoma





(Left) Radiograph shows destructive radiolucency  of the posterior mandible. Biopsy confirmed an ameloblastic carcinoma. The separation radiographically between ameloblastoma and ameloblastic carcinoma is not always possible. (Right) Subtle peripheral palisading  is seen in the epithelium of this ameloblastic carcinoma. Mitotic figures  can be seen in this medium power image.

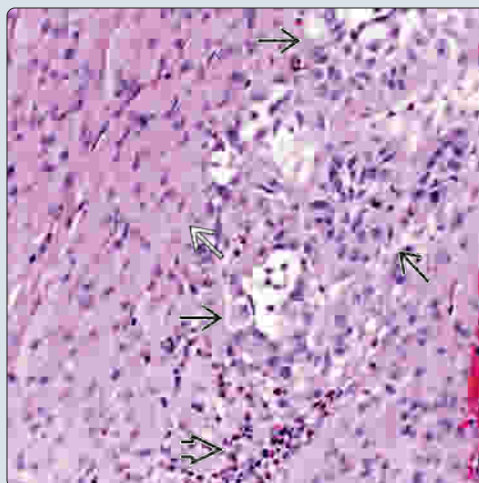


Mitotic Activity

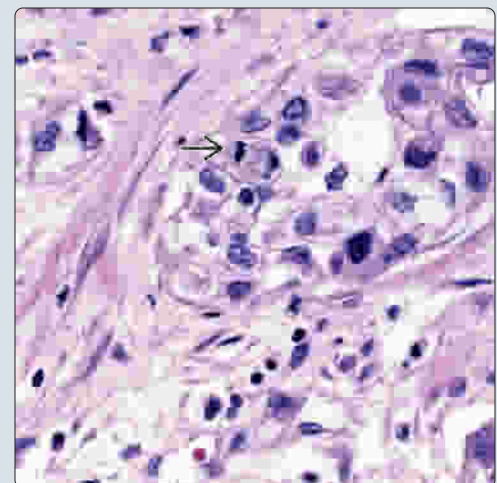


Muscular Invasion

(Left) This hematoxylin and eosin shows invasion of the tumor  into the skeletal muscle  and the inflammatory reaction  that resulted. This tumor started growing within the mandible but eventually invaded the surrounding soft tissues. (Right) This example of ameloblastic carcinoma shows increased nuclear:cytoplasmic ratio, pleomorphism, hyperchromasia, loss of cellular adhesion, and a mitotic figure .



Malignant Cytologic Features



TERMINOLOGY

Definitions

- Odontogenic tumor that shows malignant histologic features within ameloblastoma

ETIOLOGY/PATHOGENESIS

Types

- Ameloblastic carcinoma arising de novo
 - Primary tumor
- Ameloblastic carcinoma arising from intraosseous ameloblastoma (uncommon)
 - Secondary (dedifferentiated) or carcinoma ex intraosseous ameloblastoma
- Ameloblastic carcinoma arising from peripheral ameloblastoma (very rare)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Extremely rare
- Age
 - Wide range
- Sex
 - Male > female
- Ethnicity
 - May exhibit increased incidence in Chinese

Site

- Majority develop in mandible, most frequently in posterior region
- Uncommon in maxilla
- Rarely involves other skull locations: Anterior skull base and paranasal sinuses

Presentation

- Painful swelling or mass, often rapidly growing
- Ulcer or fistula formation
- Paresthesia of lower lip
- Many present with metastatic disease: Regional lymph nodes, lung, bone

Treatment

- Options, risks, complications
 - Definitive management difficult to determine due to limited case reports
 - Long-term follow-up is essential
- Surgical approaches
 - All require radical resection
 - Partial or total mandibulectomy, maxillectomy
 - Enucleation or curettage not advocated
 - Neck dissection for clinically suspicious lymph nodes

Prognosis

- Generally poor prognosis
- High recurrence rate: Highest with enucleation or curettage

IMAGING

Radiographic Findings

- Ill-defined or irregular radiolucent lesion

- Multilocular or unilocular
- Cortical expansion, frequently with perforation
 - May infiltrate into adjacent structures
- Well-defined borders

MICROSCOPIC

Histologic Features

- Ameloblastoma features
 - Peripheral palisading, reverse polarization, central stellate reticulum
 - Other features of any histological subtype of ameloblastoma
- Epithelial atypia (carcinoma)
 - Profound pleomorphism with hyperchromasia
 - Increased nuclear to cytoplasmic ratio
 - Loss of cellular adhesion
 - Mitoses are increased, including atypical forms
- Necrosis
- Vascular &/or perineural invasion

ANCILLARY TESTS

Flow Cytometry

- Aneuploidy more frequently identified in ameloblastic carcinoma than in ameloblastoma

Genetic Testing

- CGH has shown amplification of 5q13

DIFFERENTIAL DIAGNOSIS

Ameloblastoma

- Lacks cytologic atypia

Intraosseous Squamous Cell Carcinoma

- Lacks reverse polarity and basal palisading

Clear Cell Odontogenic Carcinoma

- Tumor cells are predominately clear, usually with heavy hyalinization; limited pleomorphism
- PAS with and without diastase reveals glycogen; most show *EWSR1* rearrangements

Metastatic Disease

- Lacks reverse polarity or basal palisading; known primary

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KEY FACTS

TERMINOLOGY

- Malignant epithelial odontogenic neoplasm composed primarily of clear cells

CLINICAL ISSUES

- Rare
- 75% in mandible
- Aggressive resection
- High recurrence rate

IMAGING

- Poorly defined radiolucency
- Bone destruction

MACROSCOPIC

- Invades medullary bone
- Cortical destruction
- Unencapsulated

MICROSCOPIC

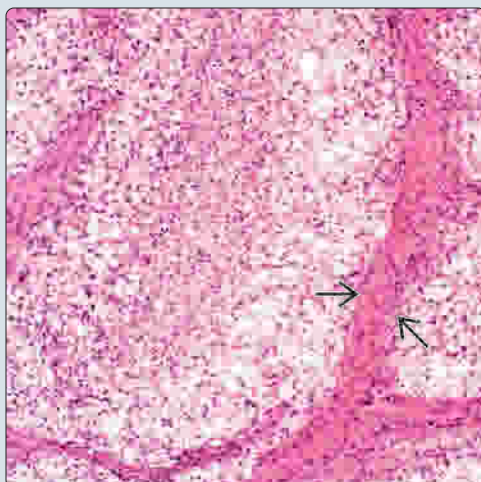
- Biphasic tumor: Epithelial islands in heavy stroma
- Small islands or nests
- Islands or cords of epithelial cells
- Polygonal cells with well-defined cell borders (cookie cutter)
- Clear to finely granular, glycogen-rich cytoplasm
- Focal peripheral palisading
- Fibrous to heavily collagenized stroma
- May have islands of other odontogenic tumors

TOP DIFFERENTIAL DIAGNOSES

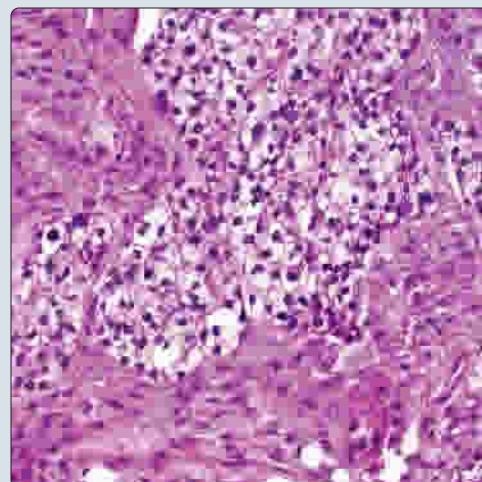
- Metastatic renal cell carcinoma
- Intraosseous mucoepidermoid carcinoma
- Clear cell variant of calcifying epithelial odontogenic tumor
- Ameloblastoma

(Left) H&E shows large tumor islands of clear cells surrounded by thickened hyalinized fibrosis [E]. Sometimes it is heavier and more collagenized than others. **(Right)** These islands of odontogenic epithelium demonstrate polygonal cells with prominent cell borders. The cells of clear cell odontogenic carcinoma are often bland in appearance. Image studies often show poorly defined radiolucencies with local destruction.

Broad Hyalinized Bands Dissect Tumor



Islands of Odontogenic Epithelium

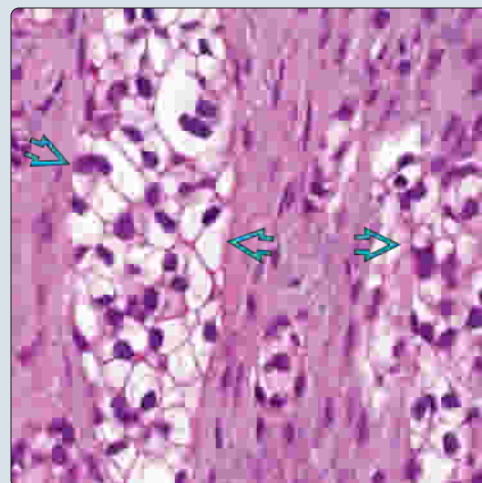


(Left) Hematoxylin & eosin shows tumor islands made up of clear cells with peripheral palisading [E]. Because of the palisading, this tumor may be misdiagnosed as an ameloblastoma. A metastatic clear cell neoplasm must also be considered, although patients will usually have a known history. **(Right)** H&E shows islands of epithelium made up of cells [E] with clear cytoplasm and oval, hyperchromatic nuclei. There is heavy stromal hyalinization.

Peripheral Palisading



Clear Cytoplasm in Neoplastic Cells



TERMINOLOGY

Abbreviations

- Clear cell odontogenic carcinoma (CCOC)

Synonyms

- Clear cell odontogenic tumor

Definitions

- Malignant epithelial odontogenic neoplasm composed primarily of clear cells

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare, with < 100 reported cases
- Age
 - Mean: 60 years; range: 17-90 years
- Sex
 - Female > male

Site

- 75% in mandible, favors anterior mandible

Presentation

- Swelling
- Loosening of associated teeth
- Pain
- Destructive mass
- Asymptomatic

Treatment

- Surgical approaches
 - Aggressive wide resection
 - Elective neck dissection
 - Reconstruction
- Adjuvant therapy
 - Radiotherapy, efficacy unknown
- Long-term follow-up

Prognosis

- High recurrence rate
- Frequent metastases: Lungs most common

IMAGING

Radiographic Findings

- Poorly defined radiolucency
- Bone destruction

MACROSCOPIC

General Features

- Unencapsulated, usually invading medullary bone
- Cortical destruction
- May infiltrate surrounding soft tissue

MICROSCOPIC

Histologic Features

- Biphasic tumor appearance
- Islands or cords of epithelial cells
 - Clear to finely granular, glycogen-rich cytoplasm

- Polygonal
- Well-defined cell borders (cookie cutter)
- Focal peripheral palisading
- Oval nuclei with vesicular to hyperchromatic nuclei
- Fibrous stroma
 - Broad hyalinized bands
 - Some tumors may appear organoid
- May have islands of other odontogenic tumors
 - Ameloblastoma
 - Calcifying epithelial odontogenic tumor

ANCILLARY TESTS

Histochemistry

- PAS-diastase
 - Reactivity: Positive to equivocal
 - Staining pattern: Cytoplasm of clear cells (focal pattern)
- Alcian blue: Negative
- Mucicarmine: Negative

Immunohistochemistry

- Of little practical use
- **Positive:** Various keratins (CK8, 5/6, 18, 13, 14, 19); p63, AE1/AE3, EMA
- **Negative:** S100 protein, SMA, HMB-45, calponin

Genetic Testing

- *EWSR1* rearrangements (detected by FISH probe)

DIFFERENTIAL DIAGNOSIS

Metastatic Renal Cell Carcinoma

- Rare; history of renal cell carcinoma
- Highly vascular
- **Positive:** pax-2, pax-8, CD10, RCC

Intraosseous Mucoepidermoid Carcinoma

- Epidermoid, intermediate and mucous cells
- Mucin-**positive** mucous cells
- May be cytologically more atypical

Clear Cell Variant of Calcifying Epithelial Odontogenic Tumor

- Psammomatous calcifications
- Amyloid deposits

Ameloblastoma

- Rare cases may have clear cells

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KEY FACTS

TERMINOLOGY

- Rare, malignant, odontogenic neoplasm; considered malignant counterpart to ameloblastic fibroma or fibro-odontoma

ETIOLOGY/PATHOGENESIS

- Upward of 40% of tumors arise from ameloblastic fibroma

CLINICAL ISSUES

- Extremely rare
- Wide range at presentation; mean: 3rd decade
- High recurrence rates, up to 45%
- Mandible most commonly affected (80%)
- Treatment: Radical resection and chemoradiation
- Overall prognosis is good, although unpredictable

IMAGING

- Bone destruction with irregular borders
- "Moth eaten"

- Expansive, multilocular radiolucencies
- May demonstrate soft tissue expansion

MICROSCOPIC

- Islands and cords of cuboidal to columnar epithelium
- Stroma is variably cellular
 - Pleomorphism
 - Hyperchromasia
 - Numerous mitotic figures
 - Storiform or herringbone pattern

ANCILLARY TESTS

- AFS shows higher Ki-67 labeling than AF (10x increase)

TOP DIFFERENTIAL DIAGNOSES

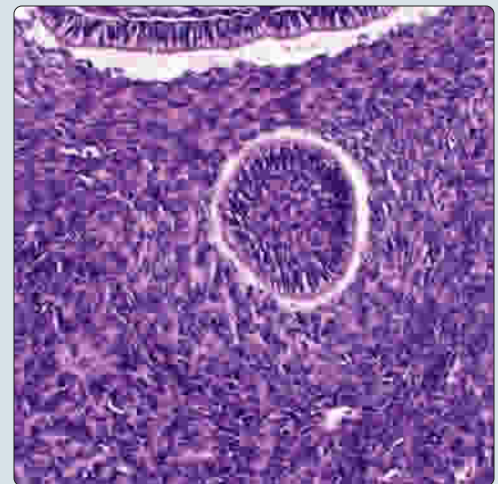
- Ameloblastic fibroma
- Ameloblastic fibro-odontoma
- Ameloblastic fibrodentinosaoma
- Ameloblastoma
- Fibrosarcoma

(Left) Ameloblastic fibrosarcoma (AFS) resembles an ameloblastic fibroma (AF) except for the highly cellular, hyperchromatic, pleomorphic stroma. This feature is easily seen at low to medium magnification. Patients affected by AFS are generally older than those affected by ameloblastic fibroma/fibro-odontoma. **(Right)** Characteristic odontogenic epithelium, similar to what is seen in ameloblastoma or AF but set within a very cellular stroma, is shown.

Highly Cellular and Atypical Stroma



Island of Epithelium in Cellular Stroma

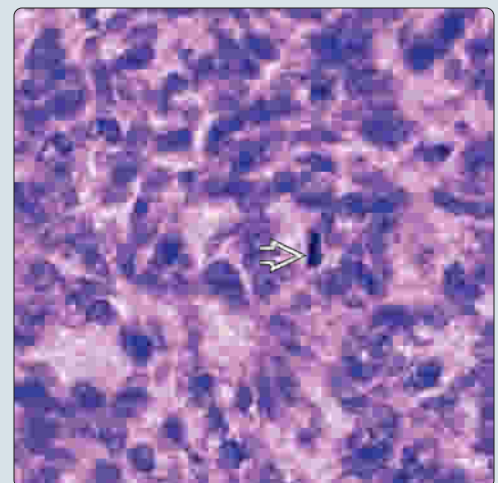


(Left) These islands of odontogenic epithelium are seen within a stroma that shows a streaming or herringbone pattern. **(Right)** AFS usually has numerous mitotic figures, one shown here. This very cellular background and mitotic figure should help separate this tumor from a benign tumor within the differential diagnoses.

Variable Stroma Patterns



Mitotic Figure in Stromal Cells



TERMINOLOGY**Abbreviations**

- Ameloblastic fibrosarcoma (AFS)

Definitions

- Rare, malignant, odontogenic neoplasm, considered malignant counterpart to ameloblastic fibroma (AF) or fibro-odontoma

ETIOLOGY/PATHOGENESIS**Pathogenesis**

- Many tumors (45%) arise from AF

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Extremely rare
- Age
 - Wide range at presentation; mean: 3rd decade
 - Found in patients older than those affected by AF (by 4-25 years)

Site

- Mandible most commonly affected (80%)
 - Posterior specifically
- Maxilla
 - Often extends into sinus

Presentation

- Pain &/or swelling
- Ulceration of associated soft tissue

Treatment

- Surgical approaches
 - Radical resection with wide surgical margins required
 - Neck dissection usually not indicated as sarcoma spread is generally hematogenous
- Adjuvant therapy
 - Combination chemoradiation is variably effective

Prognosis

- Overall prognosis is good, although unpredictable
 - AF have increased recurrence rate (20%); therefore, complete surgical excision and long-term follow-up is recommended
- High recurrence rates
- Distant metastases generally do not develop
- Death is usually from direct extension into vital structures, especially of skull base

IMAGING**Radiographic Findings**

- Bone destruction with irregular borders
 - "Moth eaten"
- Expansive, multilocular radiolucencies
 - May demonstrate soft tissue expansion
- Perforation of cortical plate
- Maxillary tumors may erode into sinus
- Rarely, pathologic fracture

MACROSCOPIC**General Features**

- Large, osteolytic tumors spreading into soft tissues

MICROSCOPIC**Histologic Features**

- Biphasic appearance is characteristic
 - Benign odontogenic epithelium within malignant mesenchymal fibrous stroma
- Islands and cords of bland cuboidal to columnar epithelium
 - Similar to ameloblastic fibroma
 - Epithelium decreases with successive recurrences
- Stroma made up of fibroblastic cells
 - Variable, but usually highly cellular
 - Storiform or herringbone pattern
 - Pleomorphism and hyperchromasia
 - Increased mitoses

ANCILLARY TESTS**Immunohistochemistry**

- Stroma **positive**: Vimentin, muscle specific actin, smooth muscle actin, p53
 - Histiocytes **positive**: CD68
- AFS shows higher Ki-67 labeling than AF (nearly 10 fold increase)

DIFFERENTIAL DIAGNOSIS**Ameloblastic Fibroma**

- More ameloblastic epithelium with less cellular stroma, lacking pleomorphism and increased mitoses

Ameloblastic Fibro-Odontoma

- Identical to AF, but with dental hard tissues

Ameloblastic Fibro-dentinosarcoma

- Similar histology, but with dentin &/or enamel
- Prognosis essentially same

Ameloblastoma

- Mature, bland collagenous stroma
- More ameloblastic epithelium
 - Variable histologic subtypes

Fibrosarcoma

- Lacks ameloblastic epithelium

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KEY FACTS

TERMINOLOGY

- Primary intramedullary high-grade malignant tumor of mesenchymal origin in which neoplastic cells produce osteoid, even if only in small amounts

CLINICAL ISSUES

- Jaws represent 4th most common site for osteosarcoma (OS)
- Gnathic OS: 4th decade
- Slow-growing mass or swelling, with increasing pain with time
- Surgery is mainstay of treatment, with **clear margins** single most important factor in curing OS
- Overall, prognosis is guarded, with 70% overall 5-year survival

IMAGING

- Best diagnostic clue: Bone destruction with aggressive periosteal reaction and tumor bone formation

- Typical sunray (sunburst) appearance at tumor leading edge

MICROSCOPIC

- Hallmark feature is production of malignant bone or osteoid by atypical osteoblasts
 - Minimal and deposited as thin, lace-like eosinophilic strands interposed between sheets of malignant osteoblasts
 - Significant osteoid and bone production forming broad trabeculae with isolated single osteoblasts
- Variants: Chondroblastic (most common in head and neck), osteoblastic, fibroblastic and telangiectatic






ANCILLARY TESTS

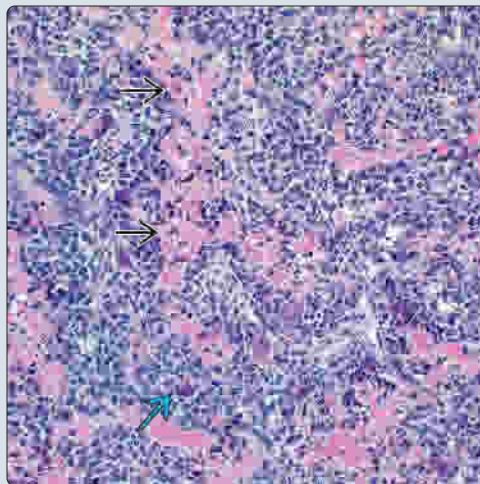
- High incidence of mutations in *RB1*, *TP53*, *CDK4*, and *MDM2*

TOP DIFFERENTIAL DIAGNOSES

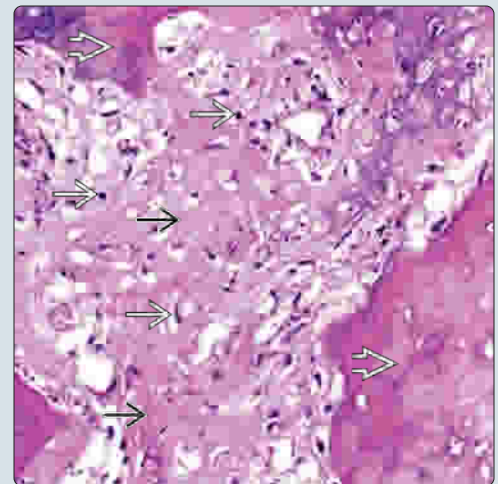
- Osteblastoma, chondrosarcoma, fracture callus, fibrous dysplasia, giant cell tumor

Lacy Osteoid in Osteosarcoma






(Left) Delicate, lace-like osteoid (pink ) is noted within a proliferation of primitive osteoblasts. Malignant osteoid is a requirement for the diagnosis. Giant cells are noted . (Right) Osteosarcoma (OS) has a malignant mesenchymal lineage. An atypical osseous matrix  arises from the neoplastic osteoblasts  infiltrating through the native trabeculae .

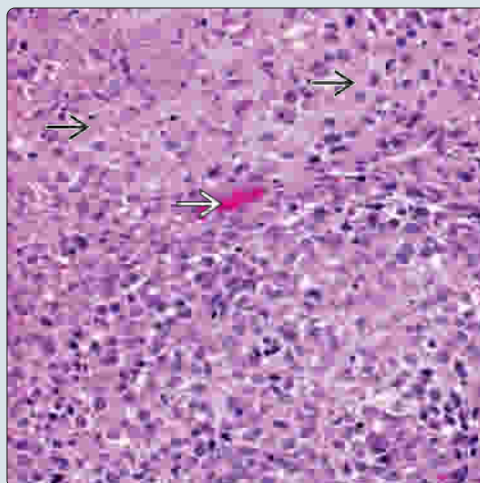


Osteosarcoma Matrix

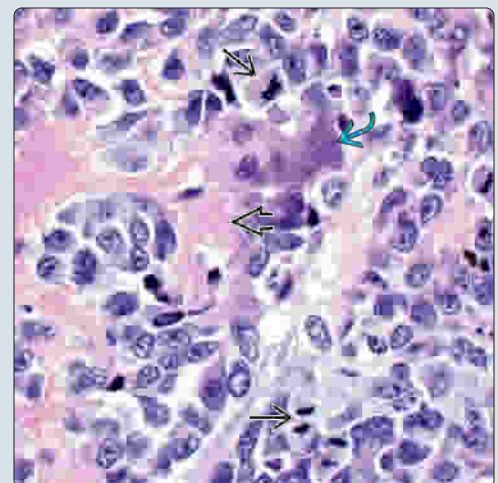


Patterns in Osteosarcoma

(Left) Histologically, OS show a wide variety of patterns. Here, a delicate, lace-like osseous matrix  arises around the pleomorphic osteoblasts. Delicate blood vessels  are also noted. (Right) Delicate, eosinophilic bone matrix  is deposited within a pleomorphic population of osteoblasts. Mitoses  are easily identified throughout. A giant cell is noted .



High-Grade Osteosarcoma



TERMINOLOGY

Abbreviations

- Osteosarcoma (OS)

Definitions

- Primary intramedullary high-grade malignant tumor of mesenchymal origin in which neoplastic cells produce osteoid, even if only in small amounts

ETIOLOGY/PATHOGENESIS

Predisposing Factors

- May develop after radiation (or chemotherapy) for other neoplasms
 - Usually 5-15 years after therapy
 - Over 10% of jaw OS is radiation induced
- Paget disease of bone and retinoblastoma
 - Retinoblastoma gene associated with some OS
- History of trauma but probably just bringing underlying lesion to clinical attention
- Osteomyelitis, osteoblastoma, osteochondroma, and fibrous dysplasia may be concurrently present but are not thought to be causative

CLINICAL ISSUES

Epidemiology

- Incidence
 - OS is rare, even though it is most common primary malignant bone tumor
 - Jaw incidence: 0.7 per million population
 - Jaws represent 4th most common site for OS
 - 6% of all OS patients
- Age
 - Sinonasal OS: 3rd-4th decades
 - Gnathic OS: 4th decade
 - Diagnosed ~ 10-20 years later than their long bone counterparts
- Sex
 - Male > female (1.5:1)

Site

- Mandible and maxilla are equally affected
 - Angle of mandible and posterior region of mandibular body
 - Most are intramedullary rather than parosteal
 - Maxilla: Canine-premolar area
- Much less common in paranasal sinuses, zygoma, or orbital ridge

Presentation

- Slow-growing mass or swelling
- Increasing pain with time
- Numbness and limitation of mouth opening
- Malocclusion and teeth loss
- Paresthesia or hypoesthesia less common
- Uncommonly present with trismus, nasal obstruction

Treatment

- Surgical approaches
 - Surgery is mainstay of treatment

- Single most important factor in curing OS is **clear margins**
 - Achieving clear margins is difficult due to anatomic constraints
- Drugs
 - Adjuvant chemotherapy commonly recommended for high-grade OS, especially if close or positive margins
 - Chemotherapy has mixed results in jaw OS
 - Most OS of jaw are chondroblastic type, which fail to respond to chemotherapy
 - < 25% response for jaw OS
- Radiation
 - OS considered radioresistant, so postoperative radiotherapy is not well defined

Prognosis

- Local recurrence rates up to 25%
 - Main reason for treatment failure and mortality
 - Maxillary tumors particularly difficult to eradicate
- Metastatic risk is high
 - Micrometastases estimated to be 80%, although lower in craniofacial OS
 - 20% of all OS patients have solid metastases when 1st diagnosed
 - Lung is most frequent site
 - Lung metastases have better prognosis than metastases in other organs
- Overall, prognosis is guarded
 - 70% overall 5-year survival
- Staging, to include chest and abdominal CT and bone scan, is required

IMAGING

General Features

- Best diagnostic clue: Bone destruction with aggressive periosteal reaction and tumor bone formation
 - Poorly defined, intramedullary mass ± tumoral calcification, showing aggressive periosteal reaction

Radiographic Findings

- Widely variable from lytic, mottled to densely sclerotic destructive lesions
 - Most lesions have associated soft tissue mass
 - Might not be obvious on conventional radiographs due to anatomy
- Variable density based on degree of neoplastic bone formation
 - Typical sunray (sunburst) appearance at tumor leading edge due to cortical erosion
 - Higher grade lesions show higher degrees of lucency
 - Moth-eaten bone with ragged lytic areas
- Poorly defined borders with varying degrees of radiolucency and radiopacity
- Tumors adjacent to teeth may cause significant tooth resorption, widening of periodontal ligament, dissolution of lamina dura, and heightened interdental reactive or malignant bone deposition

MR Findings

- Useful for soft tissue extension, medullary bone involvement, and assessing marrow spread

CT Findings

- Noncontrast CT shows expansile lesion with increased density and aggressive periosteal reaction
- Contrast enhances solid components
- CT frequently shows unsuspected soft tissue mass

Bone Scan

- Increased uptake usually present
- Useful for staging, detection of metastases, and skip lesions

MACROSCOPIC

General Features

- Irregular, poorly defined, firm tumor with gritty areas
- Tumors are of varying densities and compositions
 - Primarily osteoblastic tumors: Very hard and scirrhous
 - Chondroblastic OS: Pale blue-gray, glistening tissue areas
 - High grade: Gelatinous and myxoid areas, hemorrhagic, necrotic
 - Soft tissue extension: Variable based on tumor type

Sections to Be Submitted

- 1 section per cm of tumor, after freezing resection specimen to aid bandsaw sectioning
- Adequate sampling of surgical margins

Size

- Range: 2-15 cm, with majority < 10 cm

MICROSCOPIC

Histologic Features

- Hallmark feature is production of malignant bone or osteoid by atypical osteoblasts
 - Moderate to high degree of pleomorphism
 - High nuclear:cytoplasmic ratio
- Malignant osteoid must be present for diagnosis
 - Minimal and deposited as thin, lace-like eosinophilic strands interposed between sheets of malignant osteoblasts
 - Significant osteoid and bone production forming broad trabeculae with isolated single osteoblasts
- OS subclassified by most prominent histologic features
- Sarcomatous stroma varies in character based on tumor grade
- **Low grade**
 - Moderately cellular with minimal pleomorphism
 - Limited mitoses
 - Irregular bone and osteoid lacking lamellae
- **High grade (most jaw tumors)**
 - High cellular with closely packed spindled to polygonal cells
 - Significant pleomorphism, prominent nucleoli
 - High mitotic index, including atypical forms
 - Little to no bone formation

Histologic Subtypes

- Many variants but most common gnathic types presented
- **Chondroblastic**
 - Most common type in head and neck
 - Cartilage must be malignant to qualify, with 5-50% of tumor chondrosarcoma

• Osteoblastic

- Composed almost entirely of osseous matrix, with isolated atypical osteoblastic cells

• Fibroblastic

- 5-50% of tumor composed of atypical spindle cells

• Telangiectatic

- Large blood-filled spaces surrounded by pleomorphic cells and osseous matrix

• Parosteal

- Mild to absent pleomorphism with focal trabecular rimming
- Specific anatomic site of development: Surface or outer bone
- Characteristic early and late radiographic appearance

ANCILLARY TESTS

Cytology

- Cytologic specimens are difficult to obtain
- Cellular smears with pleomorphic spindled and rounded tumor cells
 - Basophilic cytoplasm with microvacuoles
 - Large, hyperchromatic nuclei with indented membranes
- Multinucleated tumor cells often present
- Amorphous background osteoid: Eosinophilic (alcohol fixed), magenta (air dried)

Genetic Testing

- High incidence of mutations in *RB1*, *TP53*, *CDK4*, and *MDM2*
 - Ossifying fibroma and fibrous dysplasia may overlap, suggesting these mutations are not malignant indicators
- OS may be seen in familial cancer syndromes
 - Hereditary retinoblastoma; Li-Fraumeni, Rothmund-Thomson, Bloom syndromes

DIFFERENTIAL DIAGNOSIS

Osteoblastoma

- Radiology: Circumscribed mass with sclerotic margin of smaller lesion
- Remodeling of newly formed, thick, bony trabeculae without pleomorphism or atypical mitoses
- Sheets of epithelioid osteoblasts with trabeculae rimming

Chondrosarcoma

- Chondroid and osteoid can be present in both tumors
- Lack of malignant osteoid or osteosarcoma

Fracture Callus

- Radiology is helpful in separation
- Bone formation during healing can be very reactive but has endochondral ossification and cartilage

Fibrous Dysplasia

- Radiology often very helpful in separation
- Malignant osteoid is absent

Giant Cell Tumor

- Numerous giant cells showing nuclei similar to mononuclear cells in stroma
- Malignant osteoid and atypical mitoses are absent

Classification of Osteosarcoma by Bone Location and Variant Type

Type	Variants	Grade
Central (intra medullary)	Conventional	High
	Osteoblastic	
	Chondroblastic	
	Fibroblastic	
	Rare	High
	Telangiectatic	
	Small cell	
	Epithelioid	
	Giant cell-rich	
	Osteoblastoma-like	
	Chondroblastoma-like	
Surface (juxtacortical)	Low-grade central	Low
	Parosteal	Low
	Periosteal	Intermediate
	High-grade surface	High
Extraskeletal		Low to high

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GRADING

Low Grade

- Moderately cellular with minimal pleomorphism and limited mitoses

Intermediate Grade

- Lace-like osteoid or seams of atypical osteoid infiltrating native trabeculae

High Grade

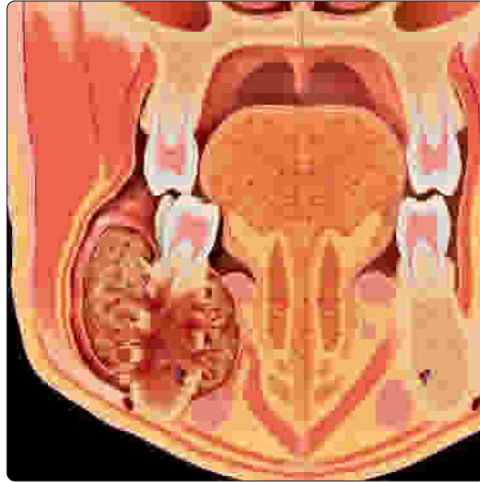
- Little to no osteoid with necrosis, increased mitoses, and significant pleomorphism

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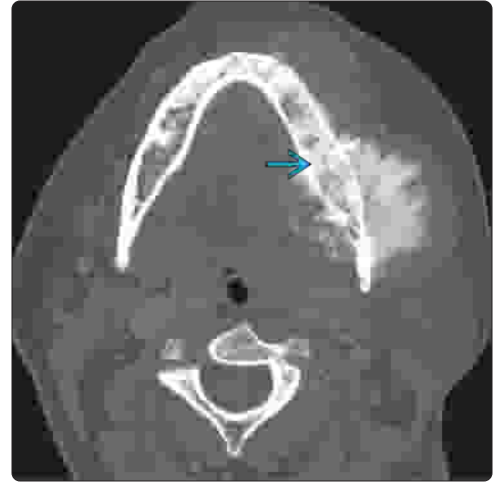
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Graphic of Mandibular Osteosarcoma

(Left) A coronal graphic shows a right mandibular body OS. There is destruction of the tooth root, with a sunburst appearance to the bony spicules. (Right) CT (bone window) shows the classic periosteal reaction associated with OS. This periosteal reaction is usually termed sunburst as the osseous matrix streams out perpendicular to the lesion. The marrow within the involved portion of the mandible is sclerotic. There is an overlying soft tissue mass.



Sunburst CT of Mandibular Osteosarcoma



Compact Bone Matrix Deposition

(Left) Axial bone CT shows an exophytic mass with amorphous immature new bone, characteristic of OS. OSs are heterogeneous in their radiologic appearance, and this case highlights a compact matrix formation. (Right) There is a flocculent appearance to rings of bony matrix deposition in this example of a maxillary sinus OS. These changes are nonspecific, however.

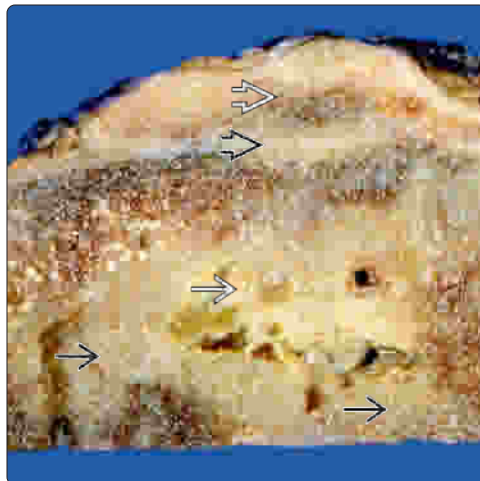


Maxillary Sinus Osteosarcoma CT

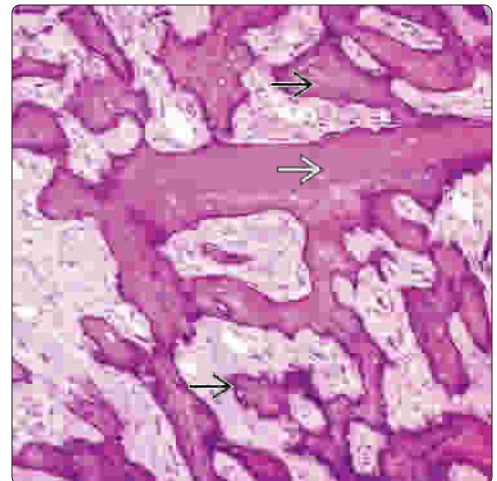


Gross Appearance of Osteosarcoma

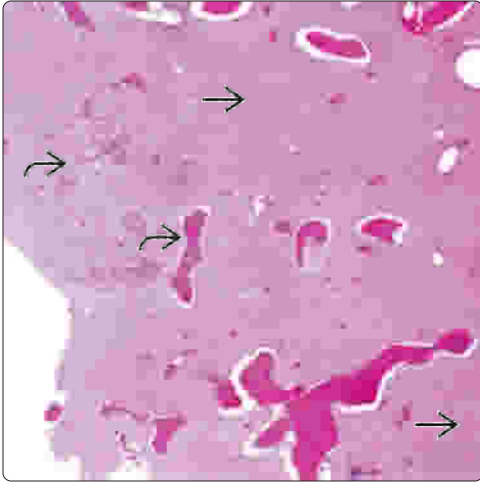
(Left) Grossly, these lesions can show dense sclerosis with areas of cystic change. These tumors often break through the overlying cortex with the development of an associated soft tissue mass. Moderately differentiated OS will demonstrate struts and islands of atypical bone that infiltrate through and around the native trabeculae. The background stroma is relatively bland in this tumor field.



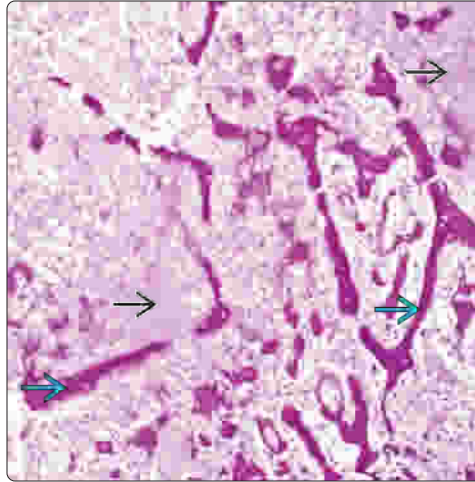
Bone Struts in Osteosarcoma



Fibrous Tissue in Low-Grade Osteosarcoma

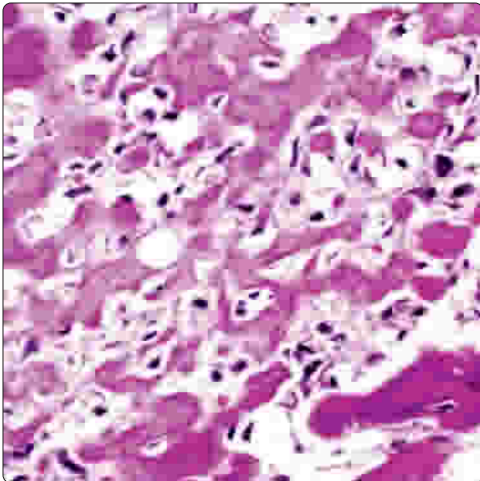


Chondrosarcoma and Malignant Osteoid

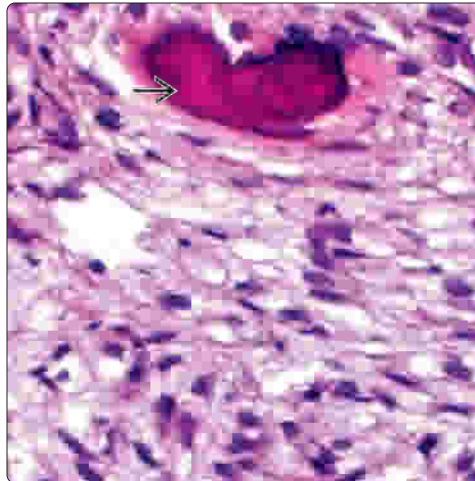


(Left) The histologic features of a low-grade OS often present as large areas of fibrous-like tissue with islands of irregularly shaped bone and osseous matrix reminiscent of fibrous dysplasia. A careful search is necessary to find the scattered atypical cells. (Right) Native trabecular bone has been infiltrated and destroyed by the matrix-producing sarcoma. There are suggestions of cartilage-type tissue, which can be seen even in nonchondroblastic OS.

Atypical Cells in Osseous Matrix

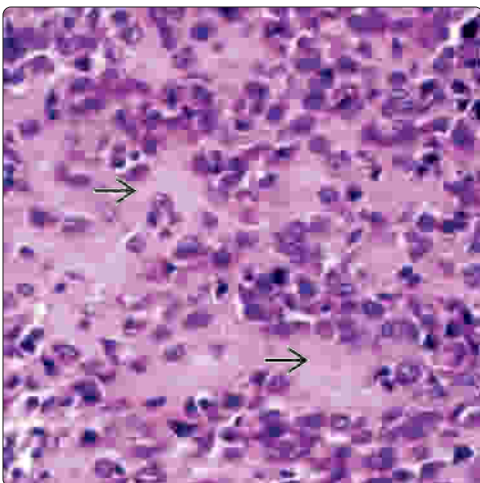


Entrapped Bone Within Osteosarcoma

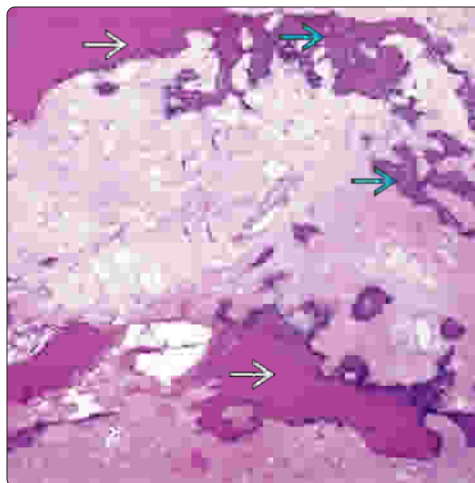


(Left) Typical OS demonstrates atypical cells of varying sizes with a readily identifiable osseous matrix. The bone lacks Haversian systems. (Right) OS shows atypical spindle cells with pleomorphism, increased nuclear:cytoplasmic ratio, and prominent nucleoli. Bone can be entrapped at the periphery or be new bone formation.

Nuclear Pleomorphism in Osteosarcoma



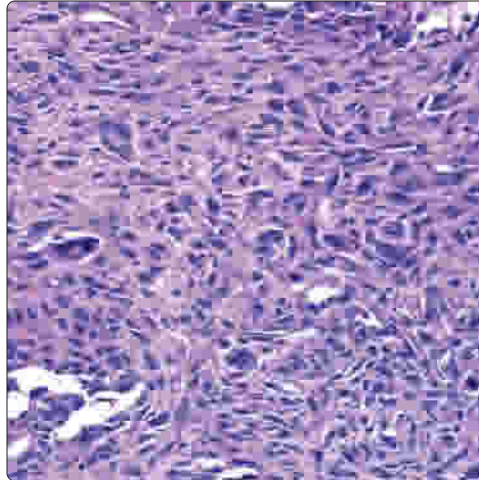
Bone Destruction by Malignant Osteoid



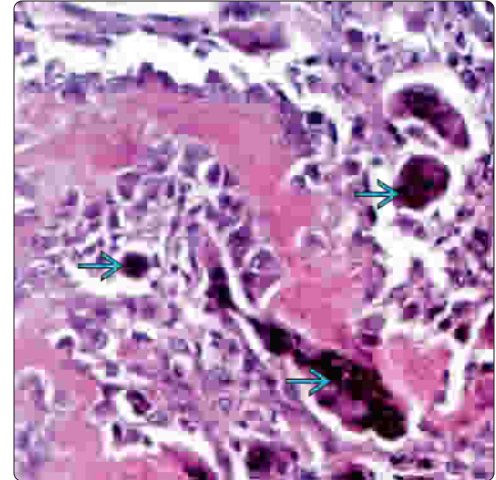
(Left) Atypical cells are noted embedded within the osseous matrix. Prominent nucleoli are noted, and apoptotic cells are abundant. The cells have a very high nuclear:cytoplasmic ratio, appearing plasmacytoid. (Right) Moderately differentiated OS infiltrates in an aggressive manner with destruction and resorption of the underlying native bone. The neoplastic bone formation can be irregularly distributed.

(Left) High-grade lesions can have little to no osseous matrix. The pleomorphism can be striking and extensive enough to suggest pleomorphic sarcoma. There will be isolated foci of recognizable OS in most cases. Immunohistochemistry is usually of little use in these lesions, but correlation with radiology is necessary. **(Right)** Tumor giant cells can be seen in OS either in apposition to the neoplastic bone formation or within the stromal matrix. Osteoclastic-type giant cells may also be seen in OS.

High-Grade Spindle Cell Population

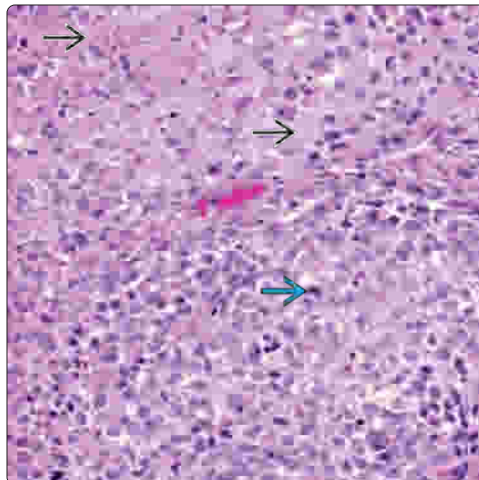


Tumor Giant Cells in Osteosarcoma

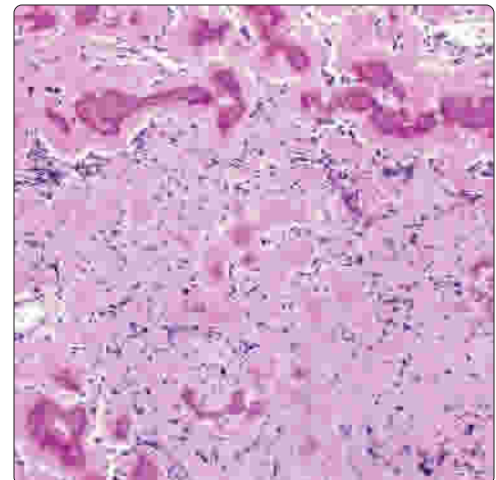


(Left) Higher grade lesions can show subtle osseous matrix. Cellularity can be quite increased and the cells can be smaller and closely packed. Mitotic figures can be seen. **(Right)** Atypical osseous matrix is deposited along with a background of heavy sclerosis. The atypical osteoblasts are squashed between the islands of bone and fibrosis.

Variable Cellularity in Osteosarcoma

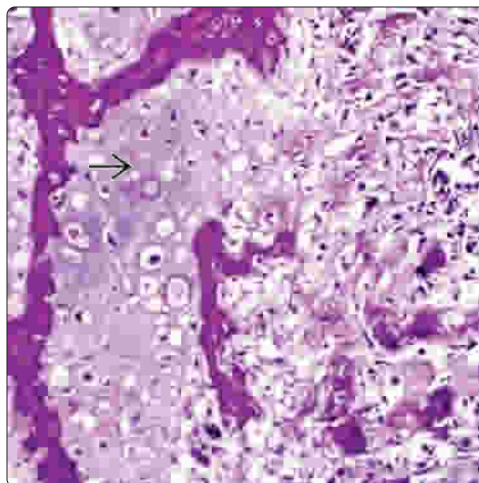


Sclerosis in Osteosarcoma

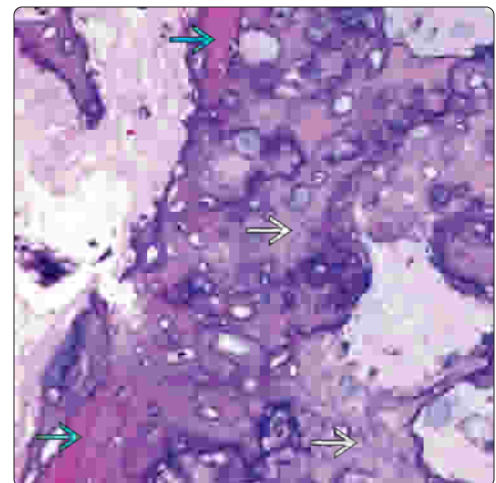


(Left) Chondroblastic OS will show features of typical OS with portions of malignant chondroid tissue where there are atypical lacunar spaces with chondrocytes. The key is to identify the matrix infiltrating the other elements. **(Right)** Chondroblastic OS is the most common type in the head and neck. These lesions often have cartilage and cartilage-like tissue proliferations in various stages of maturation. These fields are atypical and invade into and destroy the surrounding bone.

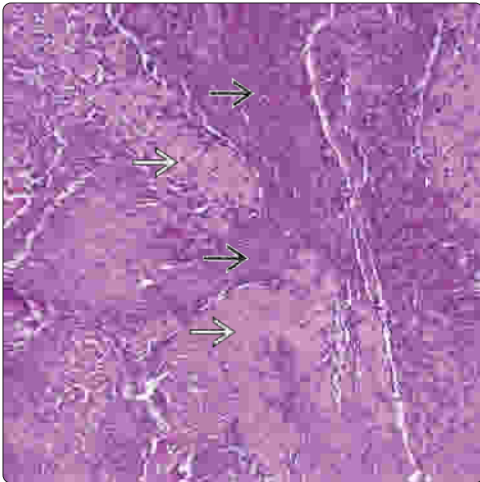
Chondroblastic Osteosarcoma



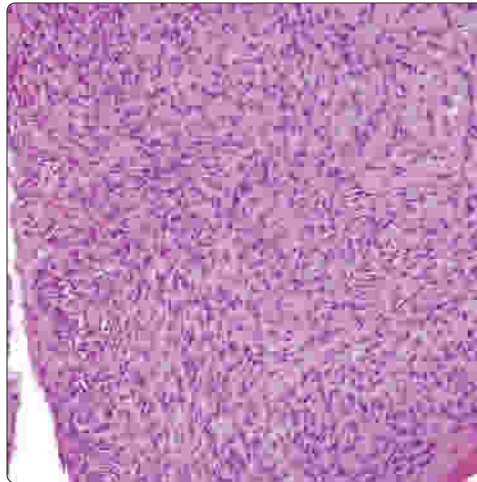
Chondroblastic Osteosarcoma



Fibroblastic Osteosarcoma

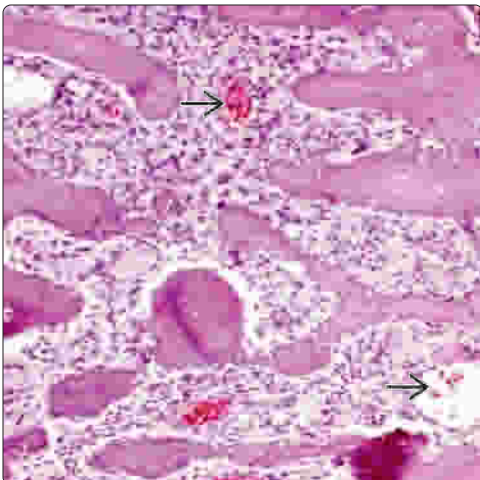


Fibroblastic Osteosarcoma

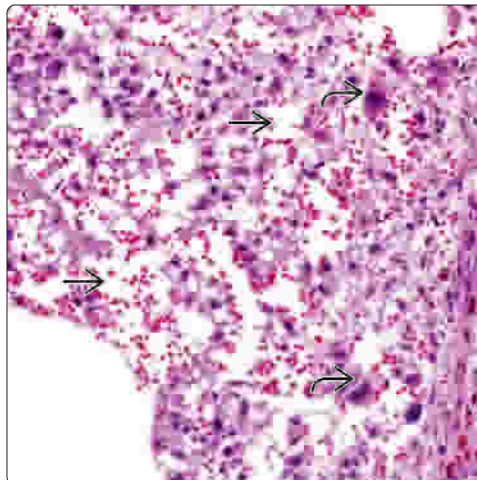


(Left) Fibroblastic OS, as its name implies, consists of spindle cell elements [] as part of the OS. Osteoid is easily identified throughout this field []. However, osteoid may need to be actively sought in some cases. (Right) Fibroblastic OS appears as a spindle cell neoplasm and can often have a paucity of matrix formation. In areas like this, the diagnosis can be difficult, necessitating adequate sampling of the lesion and correlation with the pertinent radiologic studies.

Telangiectatic Osteosarcoma

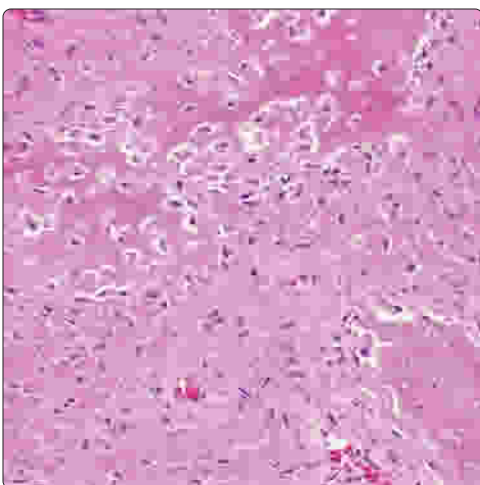


Telangiectatic Osteosarcoma

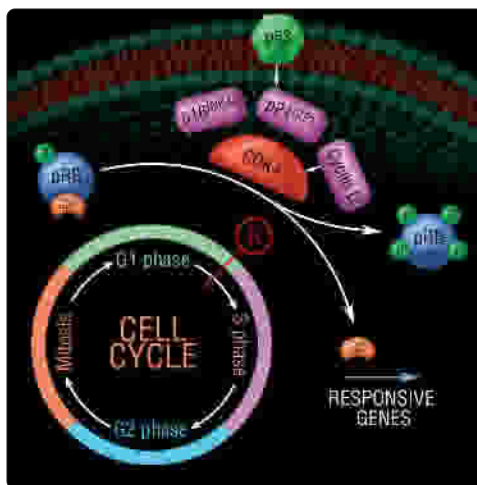


(Left) Telangiectatic OS can demonstrate areas of dense neoplastic bone formation and relatively little vascular space formation []. Adequate sampling will demonstrate the more usual features of the tumor. (Right) Telangiectatic OS often shows blood-filled spaces [] with varying amounts of blood &/or hemosiderin. Blood lakes are surrounded by large and atypical cells [], along with atypical mitoses.

Bone and Matrix in Osteosarcoma



Retinoblastoma Gene Graphic



(Left) There is osteoid matrix associated with atypical osteoblasts, both of which blend with the fibrous connective tissue in the background. Separating malignant osteoid from fibrosis can be challenging. (Right) The RB1 gene has A and B pocket domains, which bind to E2F transcription factor. Binding of the hypophosphorylated pRB to these factors represses transcription of the genes. When phosphorylated, E2F is released, and responsive genes are expressed.

KEY FACTS

TERMINOLOGY

- Chondrosarcoma (CS): Malignant mesenchymal tumor with hyaline cartilage differentiation

CLINICAL ISSUES

- Very rare in head and neck, comprising < 10% of all CSs
- Broad range; peak age at presentation: 4th decade
- Most often in maxilla and skull base
- Majority present with pain &/or swelling
- Radical surgical resection is usual treatment
- Overall prognosis: ~ 70% 5-year survival
 - Adequacy of margins important prognostic factor

IMAGING

- Best diagnostic studies: CT shows characteristic calcifications, with MR delineating extent of tumor
 - Rings and crescents of calcium most characteristic

MACROSCOPIC

- Cut surfaces have glassy to translucent, blue-white appearance, with myxoid areas

MICROSCOPIC

- No** bone formation, only destruction or entrapment by neoplastic chondrocytes
- Lobules of cartilaginous matrix, showing variability in size and shape, with irregular maturation
- Lacunar spaces contain atypical chondrocytes
- ~ 25% of mesenchymal CSs arise in jaws
- Dedifferentiated CS shows low- to intermediate-grade CS with high-grade spindle cell component (sarcoma)
- Necrosis is seen in high-grade tumors

TOP DIFFERENTIAL DIAGNOSES

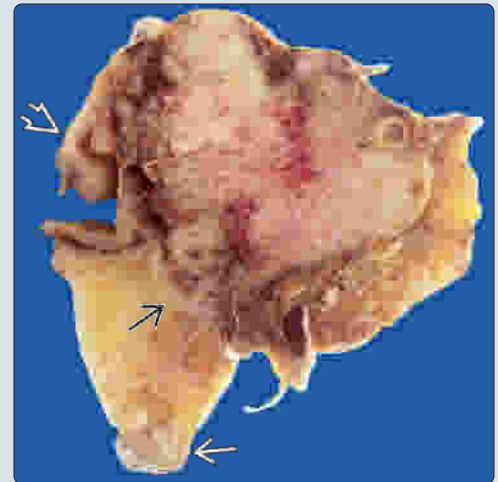
- Chondroma, chondroblastic osteosarcoma, chondromyxoid fibroma, chondroblastoma, odontogenic myxoma, chordoma, spindle cell SCC, true malignant mixed tumor

Sinonasal Chondrosarcoma

(Left) Sagittal CT shows a well-differentiated chondrosarcoma (CS) of the nasal and paranasal sinuses. The tumor is expanding and pushing the adjacent bone, extending to the skull base but without intracranial extension [1]. (Right) The resected tumor seen in the CT on cross section highlights the lobular growth pattern of the tumor. The tumor is adjacent to the sinus floor [2], filling the maxillary sinus. Sinus mucosa including the turbinates [3] are identified as well as teeth [4].

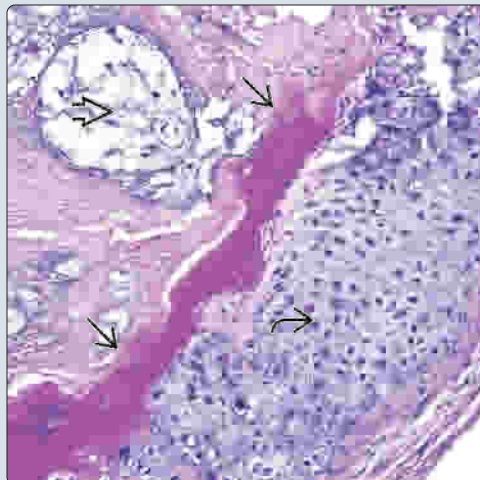


Maxillectomy Resection Gross Specimen

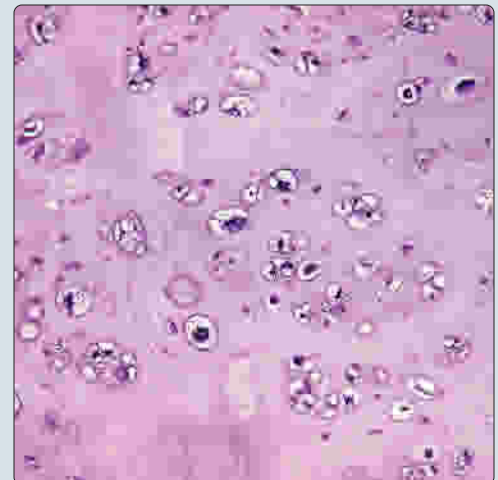


Grade 1 Chondrosarcoma

(Left) Atypical hyaline-like cartilage [1] in lobules invade through, and surround, the existing trabecular bone [2]. Myxoid degeneration [3] is often a component of these tumors. This would be considered a grade 1 tumor. (Right) There is increased cellularity with disarray of the lacunae. There is nuclear atypia, including nuclear hyperchromasia. This degree of atypia is consistent with a grade 1 tumor.



Mild Nuclear Atypia in Grade 1 Tumor



TERMINOLOGY

Abbreviations

- Chondrosarcoma (CS)

Definitions

- Malignant mesenchymal tumor with hyaline cartilage differentiation

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- May arise from cartilage or embryonal rests
 - Pluripotential mesenchymal cells

Inherited Syndromes

- Ollier disease: Enchondromas, but increased risk of CS
- Maffucci syndrome: Enchondromas and hemangiomas, but increased risk of CS

Predisposing Factors

- Ischemic change may contribute to development of CS

CLINICAL ISSUES

Epidemiology

- Incidence
 - 3rd most common primary bone tumor
 - ~ 25% of all bone tumors are CS
 - Very rare in head and neck, comprising < 10% of all CS
- Age
 - Broad range with peak age at presentation in 4th decade
- Sex
 - Male > female (1.5:1)

Site

- Most often in maxilla and skull base
- Also seen in mandible, maxillary sinus, larynx, and nasal septum

Presentation

- Majority present with pain &/or swelling
- Loose teeth
- Cranial nerve dysfunction
- Symptoms are often present for long duration due to slow growth

Treatment

- Surgical approaches
 - Radical surgical resection is preferred treatment

Prognosis

- Overall prognosis: ~ 70% 5-year survival
 - Grade 1: 90% 5-year survival
 - Grade 3: ~ 50% 5-year survival
- Vast majority of patients have grade 1 tumors
- Recurrences develop in up to 40% of cases
- Prognostic predictors
 - Adequacy of margins and resectability important in predicting biologic behavior
 - Tumor grade predicts biologic behavior
 - Pediatric patients have better prognosis than adult patients (independent of grade)

- Dedifferentiated tumors have very poor prognosis
- Metastatic disease is uncommon, but grade dependent
 - Grade 1: < 5%; grade 2: ~ 20%; grade 3: 70%

IMAGING

General Features

- Best diagnostic studies: CT shows characteristic calcifications, but MR better delineates extent of tumor
- Soft tissue mass adjacent to or involving bone with variable calcification pattern
- Presence and degree of calcification depends on tumor grade
- Erosion of bone of origin and surrounding bones

MR Findings

- **T1WI**
 - Homogeneous intermediate signal
 - Calcifications make signal heterogeneous
- **T2WI**
 - High signal (due to high water content)
 - Homo- to heterogeneous, depending on degree of calcification

CT Findings

- Radiolucent mass with lobular borders and containing scattered calcifications
- Rings and crescents of calcium most characteristic of low-grade tumors

MACROSCOPIC

General Features

- Appear as smooth, expansive, firm lesions
 - Erosion and cortical bone destruction may be seen
- Lobular appearance is common
- Areas of myxoid or mucoid material are seen
- Gritty calcifications appear as white, chalky areas

Size

- Range: 0.5-10.0 cm

MICROSCOPIC

Histologic Features

- Destruction of cancellous or cortical bone by neoplastic chondrocytes
 - Neoplastic cells invade into and replace bony tissue
 - **No** bone formation, only destruction or entrapment
- If native cartilage is present, there is abrupt transition from normal to neoplastic cartilage
- Lobules of cartilaginous matrix, showing variability in size and shape, with irregular maturation
- Lacunar spaces contain atypical chondrocytes
 - Increased nuclear hyperchromasia with stellate pleomorphic nuclei
- Bi- or multinucleation can be seen
- Mitoses are rare but can be seen in high-grade tumors
- Myxoid changes or liquefaction of cartilage is not uncommon
- Necrosis is seen in high-grade tumors
- Grading based on cellularity, nuclear size, nuclear hyperchromasia, mitoses, and necrosis

- **Types**
 - Periosteal (juxtacortical: Based on location)
 - Myxoid
 - Mesenchymal
 - ~ 25% arise in jaws
 - Even distribution between maxilla and mandible
 - Clear cell
 - Dedifferentiated
 - Dedifferentiated CS shows low- to intermediate-grade CS with high-grade spindle cell component (sarcoma)

Margins

- Clear margins decrease risk of recurrence
 - 2-3 cm of uninvolved or normal tissue is considered adequate
 - Difficult to achieve in sinonasal tract and base of skull regions

ANCILLARY TESTS

Cytology

- Cells are enlarged with increased nuclear:cytoplasmic ratio, vacuolated cytoplasm, and nuclear atypia
- Abundant chondromyxoid matrix material surrounding atypical chondrocytes
 - Cartilage matrix shows fibrillar matrix, deep magenta in air-dried preparations
 - Matrix difficult to detect on Pap-stained material

Immunohistochemistry

- **Positive** with S100 protein
- CD99(+) in small cells of mesenchymal variant

In Situ Hybridization

- HEY1-NCOA fusion protein in 75-80% of mesenchymal CS by FISH

Genetic Testing

- Complex numerical or structural chromosomal alterations
 - Loss of 13q associated with increased metastatic potential

DIFFERENTIAL DIAGNOSIS

Chondroma

- Radiographically well marginated, ranging from radiolucent to densely sclerotic lacking bone invasion
- Lacking atypia with no mitoses or necrosis

Chondroblastic Osteosarcoma

- Cartilaginous tissue in association with malignant osseous proliferation
- Osteoid is part of neoplasm (not entrapment)

Chondromyxoid Fibroma

- May show bone "entrapment" at periphery
- Lobular neoplasm with spindled cells in myxoid matrix
- Cytoplasmic extensions create fusiform or bipolar appearance
- Hyaline cartilage is identified in ~ 20% of cases

Chondroblastoma

- Remarkably uniform, cellular tumor with strong cell borders
- Pseudolobulated growth or pavement pattern

- Nuclei are often clefted or grooved, lacking atypia
- Scant to absent mature hyaline cartilage

Odontogenic Myxoma

- Myxoid matrix is dominant finding
- Hypocellular tumor with isolated islands of odontogenic epithelium

True Malignant Mixed Tumor

- Presence of both carcinoma and sarcoma within salivary gland neoplasm
- CS is most common sarcoma
- Usually has benign pleomorphic adenoma present

GRADING

Low Grade

- Relatively uniform, lobular histologic appearance resembling cartilage
- Mild increase in cellularity and rare mitoses

Intermediate Grade

- Often has myxoid-type stroma as well as hyaline-type matrix
- Cellularity is increased and will often show binucleated cells
- Multiple cells within lacunae
- Occasional mitotic figures

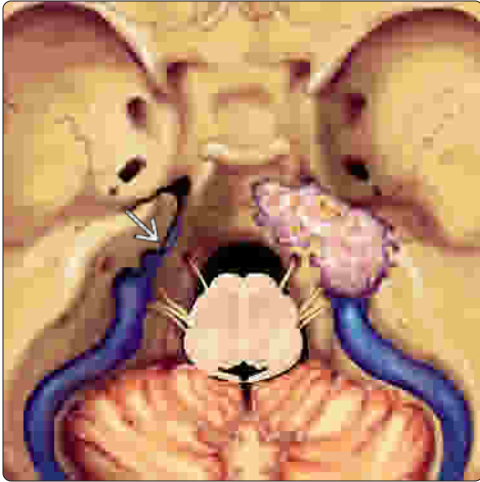
High Grade

- High cellularity with pleomorphism
- High mitotic index with atypical forms
- May have tumor necrosis

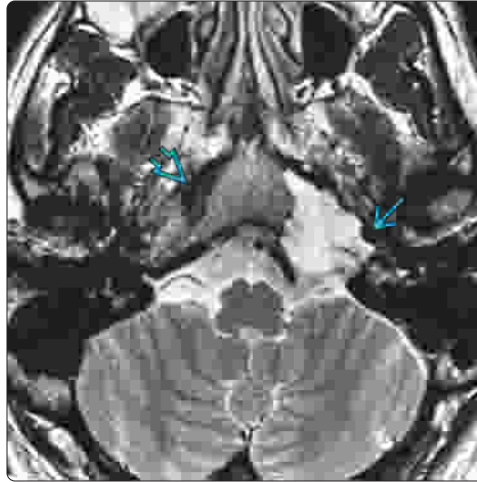
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Graphic of Skull Base Chondrosarcoma



MR of Skull Base Chondrosarcoma

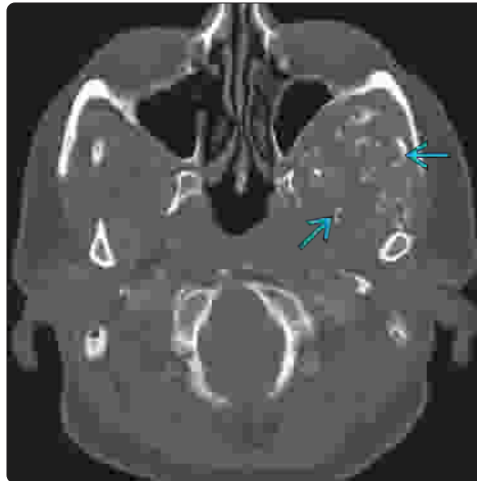


(Left) Axial graphic shows a CS in the skull base, centered in the left petrooccipital fissure. Note the calcifications within the lesion. The normal right petrooccipital fissure is also shown. (Right) Axial T2WI MR reveals high signal CS of the petrooccipital fissure. Note that the vertical segment of petrous internal carotid artery is compressed and that the right petrooccipital fissure appears normal.

Chondrosarcoma of Infratemporal Fossa

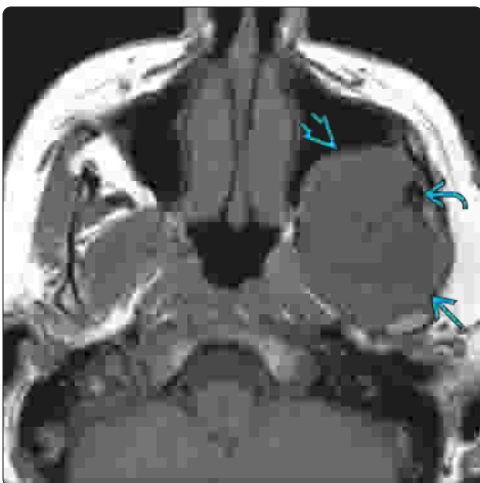


Crescent Calcifications of Chondrosarcoma

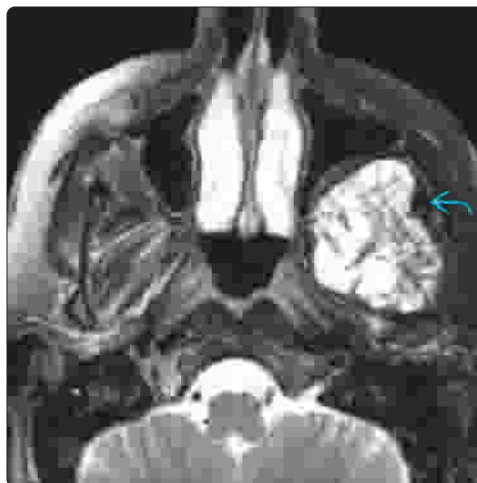


(Left) Axial CECT on a soft tissue window shows an inherently low-density mass with intrinsic calcifications that fills the left infratemporal fossa. The calcifications are fluffy, with rings and arcs. These changes are characteristic of a CS radiographically. (Right) Axial CECT viewed with a bone window shows a soft tissue mass filling the masticator space. There are rings and crescents of calcification, quite characteristic of CS.

MR of Maxillary Sinus Chondrosarcoma



Chondrosarcoma: Bright T2WI on MR



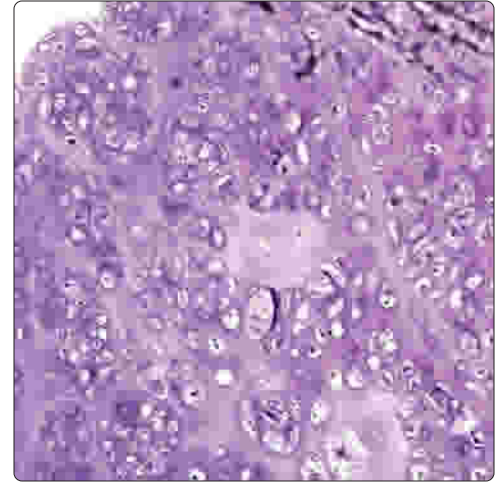
(Left) T1WI MR demonstrates a mass distending the masticator space and bowing the posterior wall of the left maxillary sinus anteriorly. A large focal calcification is seen as low signal intensity. (Right) T2WI MR demonstrates the characteristically bright signal intensity of chondroid tumors. A large focal calcification is seen as low signal intensity. The tumor is generally heterogeneous with intense enhancement with gadolinium.

Cricoid Cartilage Chondrosarcoma

(Left) Gross photograph of a well-differentiated CS arising in the cricoid cartilage of the larynx. The cut surface is blue-white with a somewhat translucent appearance. The tumor is lobulated and causes expansion of the cricoid. An infiltrative pattern is evident with tumor extending into the ossified cartilage [E]. (Right) A well-differentiated CS characterized by lobules of atypical chondrocytes with hyperchromatic nuclei and nuclear pleomorphism in a chondroid background.



Grade 1 Chondrosarcoma



Mandibular Chondrosarcoma

(Left) There is a multilobular mass causing significant distortion of the mandible, resulting in teeth displacement. The surface epithelium is intact. This tumor proved to be a CS on histologic examination. (Right) A maxillary CS shows abutment against the tooth [E]. The tumor shows increased cellularity with nuclear atypia. There are multiple areas showing bi- and multinucleation [E]. The chondroid matrix is easily identified.

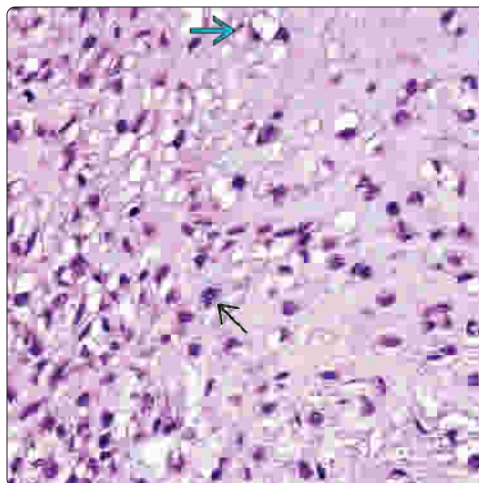


Binucleated Cells in Chondrosarcoma

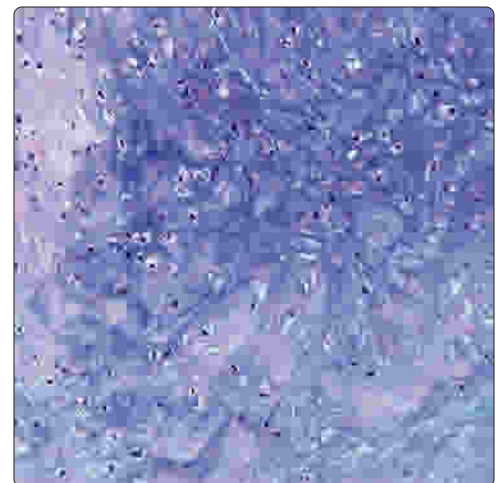


Grade 2 Chondrosarcoma: Atypical Mitoses

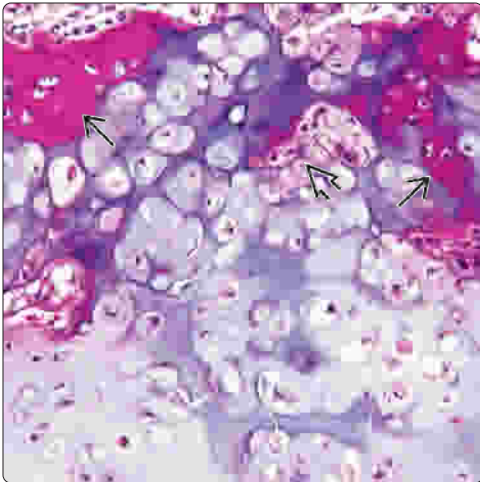
(Left) This neoplasm shows increased cellularity with cellular enlargement, filling the lacunar spaces. Bi- and multinucleation is present [E] with prominent nucleoli. An atypical mitotic figure [E] is noted within this tumor. This tumor would be interpreted as a grade 2. (Right) This myxoid variant of CS shows neoplastic chondrocytes suspended in a marked myxoid matrix. The nuclei are markedly hyperchromatic.



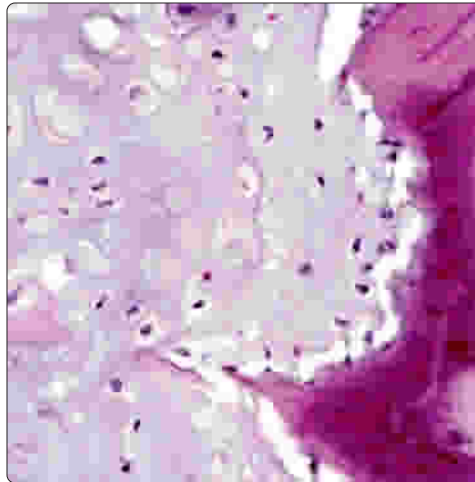
Myxoid Chondrosarcoma



Transition to Neoplastic Cartilage

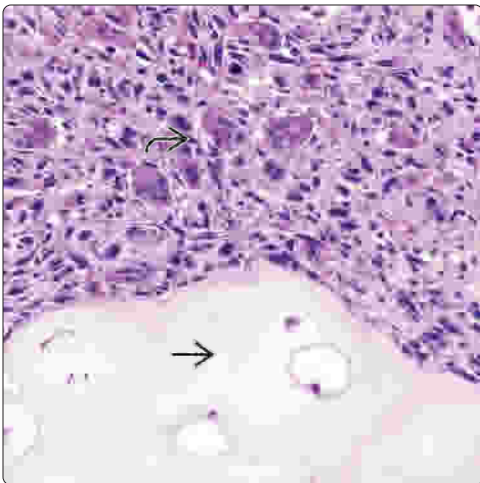


Bone Invasion and Destruction

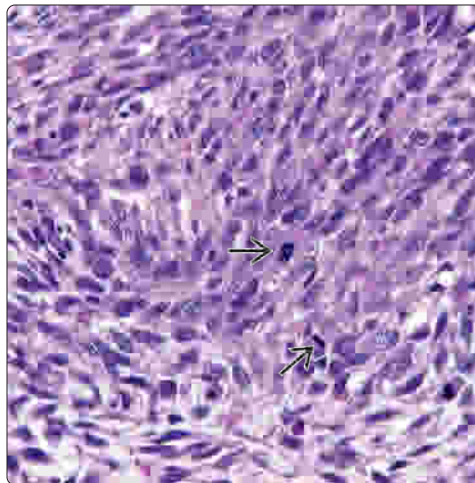


(Left) The highly atypical chondrocytes are within lacunae. There is destruction of bone tissue, which is noted at the periphery [1]. Native cartilage is also present, showing "abrupt" transition to the neoplastic foci [2]. **(Right)** The neoplastic cartilage invades and destroys bone, often producing a serrated edge to the bone. Evaluation of the cytology is done only when the biology of the lesion is established.

Dedifferentiated Chondrosarcoma

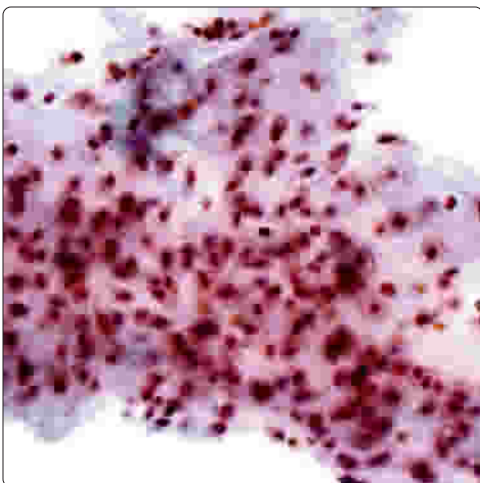


Spindle Cells in Dedifferentiated Chondrosarcoma



(Left) Dedifferentiated CS can sometimes show giant cell tumor [1] in association with the low-grade chondrosarcomatous elements [2]. The tumor cell spindling is focally noted in this field. **(Right)** Dedifferentiated CS is diagnosed when there is CS and a high-grade spindle cell component. The spindle cell component is similar to that seen in undifferentiated pleomorphic sarcoma or fibrosarcoma. Pleomorphism is extensive. Mitotic figures, including atypical forms, can be seen [3].

High Cellularity in Fine-Needle Aspiration Smears



Magenta Matrix in Air-Dried Fine-Needle Aspiration Smears



(Left) Fine-needle aspiration specimen of a jaw mass shows a highly cellular tumor with many lacunar spaces. Nuclear atypia is noted, including binucleation. Mitotic figures are not appreciated. These results can suggest a cartilage lesion, but correlation with radiology is necessary. **(Right)** Cytologic preparations often show a mucopolysaccharide background with isolated cells [1]. There is an increase in the nuclear:cytoplasmic ratio. The magenta chondroid matrix is quite characteristic on a Diff-Quik preparation.

KEY FACTS

TERMINOLOGY

- Malignant mesenchymal spindled cell tumor of fibroblasts with fascicular architecture and variable collagen matrix production

CLINICAL ISSUES

- Primary jaw lesions are rare: Up to 6% of all primary bone fibrosarcoma
- Mean age: 2nd-6th decades
- Male > Female (1.6:1.0)
- Presents with swelling, pain, paresthesia, loose teeth, mucosal ulceration
- Most common in mandible (posterior) > > > maxilla
- Radical surgery is best treatment

IMAGING

- Radiolucent, geographical, moth-eaten, or permeative bone destruction without matrix production

MICROSCOPIC

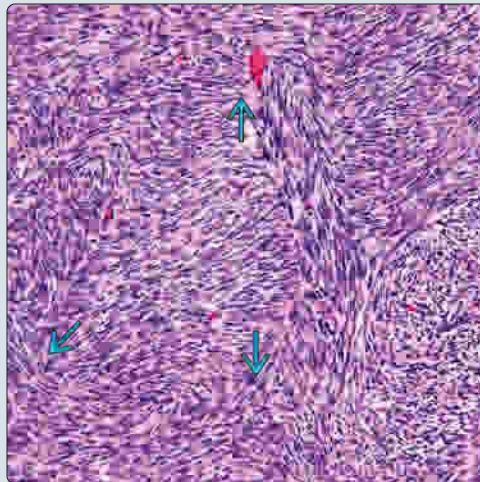
- Uniform spindle cells distributed in interlacing fascicles
 - Herringbone pattern
- Positive: Vimentin
- Fusiform cells, centrally placed, hyperchromatic, needle-spaced nuclei
- Delicate, thin to dense, keloid-like collagen deposition

TOP DIFFERENTIAL DIAGNOSES

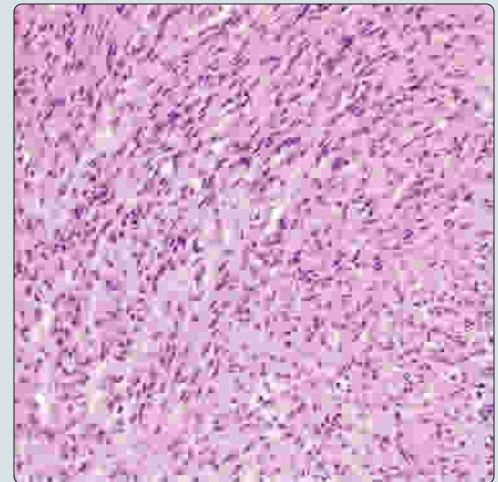
- Fibromatosis: Bland cytologic appearance with abundant collagen production
- Undifferentiated pleomorphic sarcoma: High degree of pleomorphism with vimentin staining only
- Leiomyosarcoma: Ovoid nuclei with cigar shape, perinuclear clearing, and **positive** muscle markers
- Mucosal melanoma: May be spindled, **positive** for melanocytic markers
- Spindle cell squamous cell carcinoma: May have epithelial areas and **positive** keratin markers

Herringbone Interlacing Fascicles

(Left) A herringbone pattern yields short, interlacing, acute-angle junctions to the fascicles of tumor cells. The nuclei are short, tapered, and hyperchromatic. There is a syncytial appearance. (Right) Fascicles of spindle cells are arranged in a loose bundle. The nuclei are fusiform, surrounded by eosinophilic cytoplasm. The stroma contains collagen with small delicate vessels.

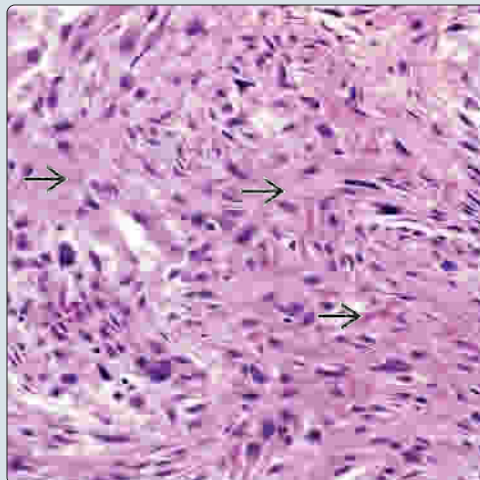


Low-Grade Fibrosarcoma

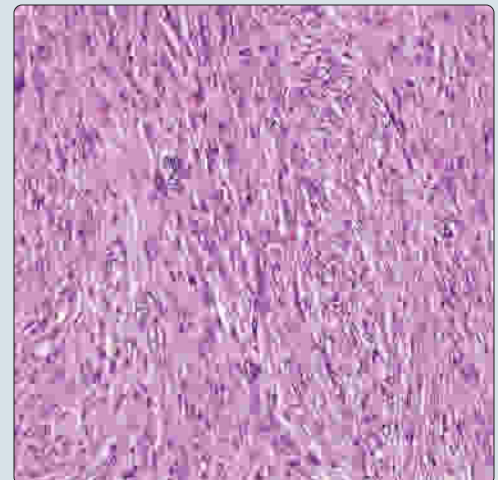


Keloidal-Like Collagen

(Left) In some fields, the collagen production can be more noticeable and give a clue as to the cell of origin. Mitoses may be present but are often difficult to find; no mitoses are seen in this field. (Right) Histologically, leiomyosarcoma is 1 of the main differential diagnostic considerations for fibrosarcoma. In the leiomyosarcoma depicted here, the cells have nuclei that display a relatively cleared chromatin rather than the darker nuclei of fibrosarcoma, often with perinuclear vacuoles.



Leiomyosarcoma



TERMINOLOGY

Definitions

- Malignant mesenchymal spindled cell tumor of fibroblasts with fascicular architecture and variable collagen matrix production

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- No etiologic factor identified but radiation-induced fibrosarcomas are recognized, albeit rare, complication of radiation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Primary jaw lesions are rare
 - Up to 6% of all primary bone fibrosarcoma
- Age
 - Mean: 2nd-6th decades
 - Rare before 3rd decade, except for infantile type
- Sex
 - Male > female (1.6:1.0)

Site

- Most common in mandible (posterior) > > > maxilla

Presentation

- Swelling is most common symptom
- May be associated with
 - Pain, paresthesia, loose teeth, mucosal ulceration

Treatment

- Surgical approaches
 - Radical surgery is best treatment
- Adjuvant therapy
 - Adjuvant radio- &/or chemotherapy is questionable
 - Often used in high-grade tumors, which may have subclinical or microscopic metastases at time of diagnosis

Prognosis

- Highly dependent on histologic grade and success of complete resection
- Overall survival: 83% at 10 years in low-grade tumors; 34% at 10 years in high-grade tumors

IMAGING

Radiographic Findings

- Radiolucent lesions
 - Geographical, moth-eaten, or permeative pattern of bone destruction
 - No internal matrix production
 - Soft tissue invasion is detected in up to 86% of cases

MACROSCOPIC

General Features

- Usually tan to grayish-white, rubbery, without matrix production ranging in size 3-15 cm
- High-grade lesions may have hemorrhage &/or necrosis

MICROSCOPIC

Histologic Features

- Uniform spindle cells distributed in compact, interlacing fascicles
 - Herringbone pattern: Acute angle intersection of cell bundles
 - Cellularity between and within tumors is variable
 - Fusiform cells, centrally placed; hyperchromatic, needle-spaced nuclei
 - Tapered cytoplasm, creating syncytial appearance
- Delicate thin to dense keloid-like collagen deposition

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** Vimentin; may have focal reactivity with CD68, CD13, lysozyme, S100 protein, NSE, CD34, CD1, CD2, CD4, CD24, CD30, desmin, EMA
- **Negative:** Muscle markers

DIFFERENTIAL DIAGNOSIS

Fibromatosis

- Bland cytologic appearance with abundant collagen production

Undifferentiated Pleomorphic Sarcoma

- High degree of pleomorphism with vimentin staining only

Leiomyosarcoma

- Ovoid nuclei with cigar shape, perinuclear clearing, and muscle markers immunohistochemically

Mucosal Melanoma

- May be spindled; **positive** for melanocytic markers

Spindle Cell Squamous Cell Carcinoma

- May have epithelial areas and keratin immunoreactivity

GRADING

Low Grade

- Herringbone arrangement of spindled cells with low to moderate cellularity, mild pleomorphism, and rare mitoses separated by collagenous stroma

High Grade

- Increased cellularity, moderate to severe pleomorphism, atypical mitoses, and necrosis

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KEY FACTS

TERMINOLOGY

- Malignant monoclonal plasma cell disorder characterized by osteolytic bone lesions, anemia, hypercalcemia, and renal failure

CLINICAL ISSUES

- Accounts for 1% of all malignant tumors, ~ 13% of hematologic malignancies
- Solitary and extraosseous plasmacytoma each make up 3-5% of plasma cell neoplasms
- Different combination regimens are used depending on patient condition and tumor risk status
- Stem cell (autologous) transplant used in patients both as first-line treatment and for those who have failed chemotherapy

MICROSCOPIC

- Monotonous sheets of neoplastic plasma cells with little normal host tissue

- Plasma cell morphology generally recognizable unless cells are poorly differentiated (plasmablastic or anaplastic)
- May see amyloid deposits presenting as acellular eosinophilic deposits



ANCILLARY TESTS

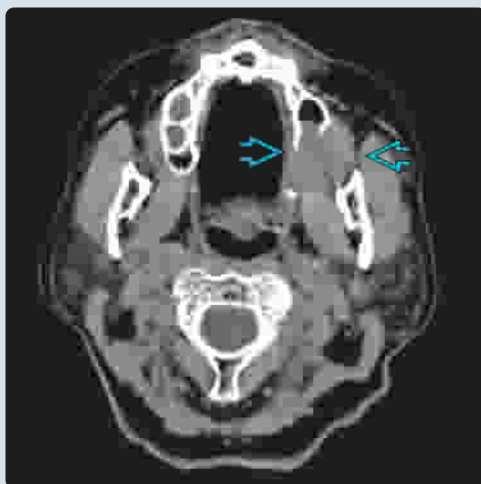
- **Positive:** CD138, CD79a; κ/λ light chain restriction to confirm monoclonal plasma cell population
- ~ 1/3 of cases exhibit chromosomal abnormalities, including deletions, trisomies, and translocations
- t(4;14), t(14;16), and 17p- have worse prognosis

TOP DIFFERENTIAL DIAGNOSES

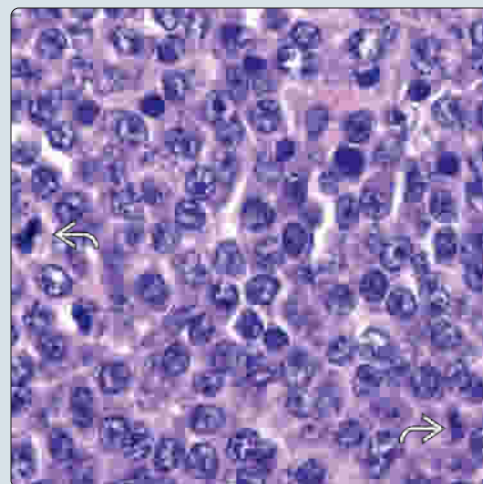
- Lymphomas with plasmacytic differentiation
 - Includes MALT and B-cell lymphoma
 - Flow cytometry, FISH, and cytogenetics may be required for diagnosis as well as clinical, laboratory, and radiographic correlation

Recurrent Multiple Myeloma on CT

(Left) Axial CT through the maxilla  shows a patient with a recent history of an enlarging maxillary alveolus preventing denture placement. The patient had been treated for multiple myeloma 5 years prior. (Right) A biopsy of a maxillary soft tissue mass reveals sheets of mature and immature plasma cells characterized by eccentrically placed nuclei and stippled chromatin with moderate amount of cytoplasm. Occasional mitoses are seen . Amyloid deposits may be identified, highlighted by Congo red.

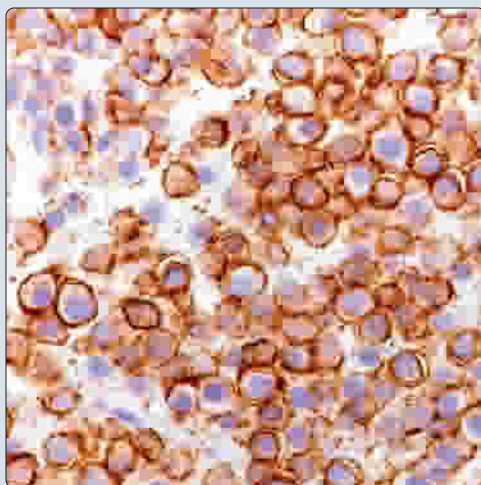


Diffuse Infiltrate of Atypical Plasma Cells

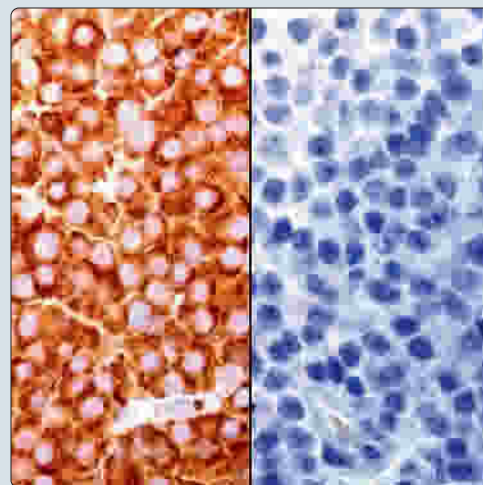


CD138 Positivity Highlights Plasma Cells

(Left) CD138 is a highly specific marker for plasma cells and is used to quantitate and differentiate plasma cells. Both cell membrane and cytoplasmic staining can be seen. LCA and B-cell marker CD20 is usually negative, while CD79-a, CD19 and CD38 are positive. (Right) There is diffuse cytoplasmic κ light chain immunoreactivity (left) with absent λ light chain reaction (right) confirming the presence of a monoclonal plasma cell population. A κ/λ ratio of > 10:1 (or the reverse) confirms the diagnosis.



κ Light Chain Restriction



TERMINOLOGY

Abbreviations

- Plasma cell myeloma (PCM)

Synonyms

- Multiple myeloma, plasma cell dyscrasia

Definitions

- Malignant monoclonal plasma cell disorder characterized by osteolytic bone lesions, anemia, hypercalcemia, and renal failure
 - Solitary plasmacytoma of bone (P-bone): Monoclonal population of plasma cells localized to 1 site without bone marrow involvement
 - Extraosseous (extramedullary) plasmacytoma (P-extraosseous): Plasma cell neoplasm arising in nonbony sites
- Consists of at least 6 nonoverlapping cytogenetic subtypes

CLINICAL ISSUES

Epidemiology

- Incidence
 - Accounts for ~ 1% of all malignant tumors and ~ 13% of hematologic malignancies
 - Solitary and extraosseous plasmacytoma each make up 3-5% of plasma cell neoplasms
- Age
 - PCM: Median age: ~ 65 years
 - P-bone and P-extraosseous: Median age: 55 years
- Sex
 - PCM: Male > female (1.5:1)
 - P-bone: Male >> female (3:1)
 - P-extraosseous: Male >>> female (6:1)
- Ethnicity
 - Black > white (2:1)

Site

- PCM: Generalized bone marrow involvement
- P-bone: Spine, ribs, skull, pelvis
- P-extraosseous: 80% occur in upper respiratory tract (URT) (paranasal sinuses, oropharynx)

Presentation

- Bone pain is most common symptom
- Later symptoms include anemia, renal failure, weakness, headache, neuropathies, visual changes

Laboratory Tests

- M-protein in serum or urine (Bence-Jones protein)
- Hypercalcemia, elevated creatinine, hyperuricemia, hypoalbuminemia, high ESR

Natural History

- Up to 2/3 patients with P-bone develop additional lesions or evolve to generalized myeloma
- ~ 70% of patients with P-extraosseous remain disease free at 10 years

Treatment

- Surgical approaches
 - Debulking of solitary soft tissue disease in URT

- Adjuvant therapy
 - Different combination regimens are used depending on patient condition and tumor risk status
- Radiation
 - P-bone and P-extraosseous: Local radiation therapy
- Stem cell (autologous) transplant used in patients both as first-line treatment and for those who have failed chemotherapy

Prognosis

- PCM is considered incurable: 3-year survival: > 75%

IMAGING

Radiographic Findings

- Multiple, punched-out or ragged lytic lesions
- Soft tissue masses seen in P-extraosseous

MICROSCOPIC

Histologic Features

- Monotonous sheets of neoplastic plasma cells with little normal host tissue
 - Eccentric nuclear placement with clockface chromatin and accentuated hof zone (Golgi apparatus)
- Plasma cell morphology generally recognizable unless poorly differentiated (plasmablastic or anaplastic)
- Mitoses variable
- May see amyloid deposits

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** CD138 (most sensitive/specific), CD79-a, CD38
- κ/λ light chain restriction to confirm monoclonal plasma cell population

Flow Cytometry

- Useful for determining immunophenotype
- Ploidy analysis: Hypodiploid has worse prognosis

Genetic Testing

- ~ 1/3 of cases exhibit chromosomal abnormalities, including deletions, trisomies, and translocations
- t(4;14), t(14;16), and 17p- have worse prognosis

DIFFERENTIAL DIAGNOSIS

Lymphomas With Plasmacytic Differentiation

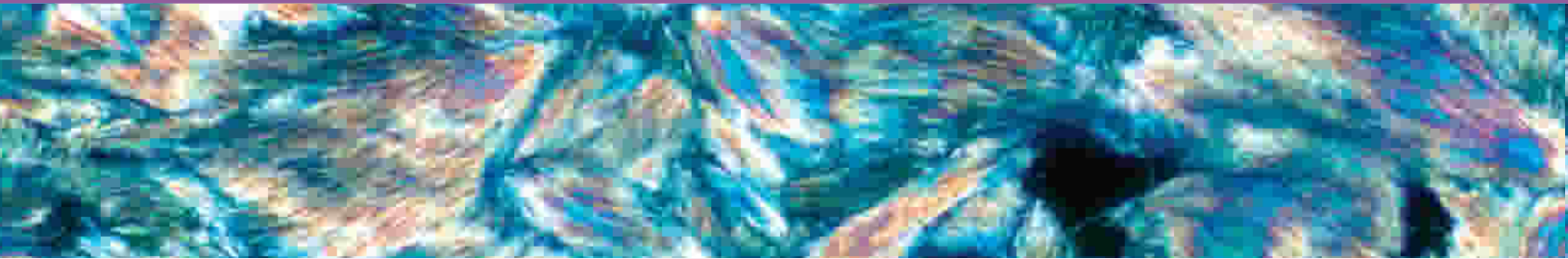
- Includes MALT and B-cell lymphoma
- Flow cytometry, FISH, and cytogenetics may be required for diagnosis as well as clinical, laboratory, and radiographic correlation

SELECTED REFERENCES

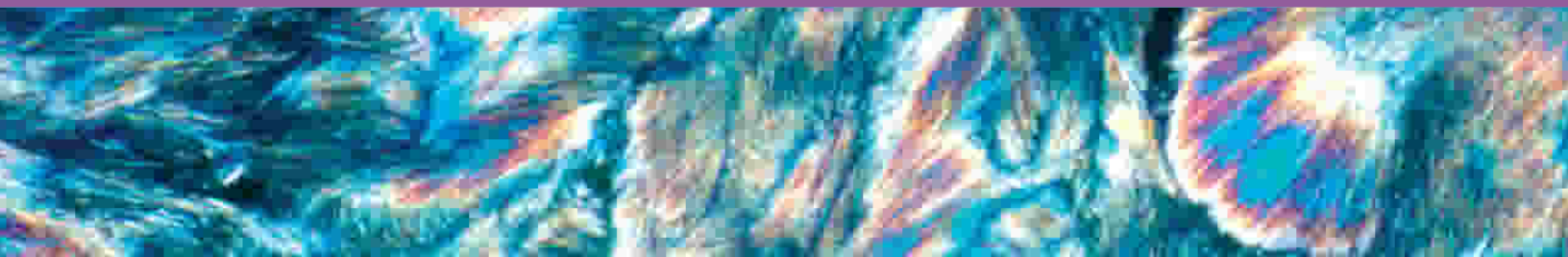
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SECTION 7

Ear and Temporal Bone



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MACROSCOPIC ANATOMY

3 Regions

- External ear: Auricle (pinna), external auditory canal (EAC), and outer surface of tympanic membrane
 - Main function is sound conduction
- Middle ear: Tympanic cavity, inner surface of tympanic membrane, ossicles, mastoid air cells, and internal auditory canal (IAC, eustachian tube)
 - Main function is sound conduction for auditory portion of inner ear
- Inner ear: Membranous labyrinth within medial petrous temporal bone (osseous labyrinth), consisting of cochlea, semicircular canals, vestibule (sacculle and utricle), and endolymphatic sac organ
 - Main functions are sensory reception for hearing and balance

MICROSCOPIC ANATOMY

External Ear

- Auricle: Modified skin structure with cartilaginous skeleton and normal skin adnexal structures
- Outer 1/3 of EAC: Supported by cartilage continuous with auricular elastic cartilage and has modified apocrine glands (ceruminous glands) instead of eccrine glands
- Inner 2/3 of EAC: Lined by epidermis typically devoid of adnexal structures/glands and supported by portions of temporal bone instead of cartilage
- Tympanic membrane: Covered by epidermis externally and nonsquamous cuboidal epithelium internally with connective tissue center

Middle Ear

- Tympanic cavity: Lined by modified respiratory epithelium consisting of single layer of cuboidal epithelium
 - No glands or squamous epithelium present under normal circumstances but may have patches of ciliated columnar epithelium
- Ossicles: Composed of compact lamellar bone

- Incudomalleolar and incudostapedial joints are diarthroses with synovial lining
- Malleus, incus, and stapes (lateral to medial)
- Mastoid air cells: Lined by flat cuboidal modified respiratory epithelium adherent to underlying periosteum
- Proximal 1/3 of IAC: Intraosseous
- Distal 2/3 of IAC: Surrounded by hyaline cartilage
- IAC: Lined by ciliated columnar epithelium; goblet cells and seromucous glands can be seen mainly in cartilaginous component
- Lymphoid aggregates (tubal tonsil): Can be seen in IAC, especially in children

Inner Ear

- Semicircular canal, utricle, and sacculle: Lined by specialized epithelia with specialized sensory hair cells (rarely, if ever, seen in surgical specimen)
- Endolymphatic sac organ: Lined by low cuboidal to columnar epithelium, which may have papillary structures in the sac portion
- Cochlea: Highly specialized, complex sensory organ that is rarely, if ever, seen in surgical specimen

PITFALLS/ARTIFACTS

Chronic Otitis Media

- Can result in glandular metaplasia (tunnel clusters), which may mimic gland-forming neoplasms
 - Primarily neuroendocrine adenoma of middle ear

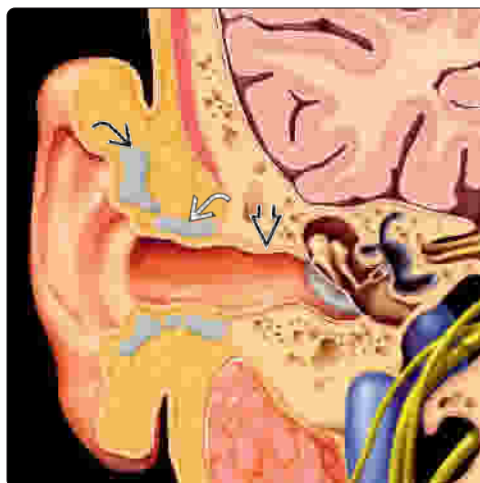
Squamous Metaplasia in Middle Ear Cavity






- Always abnormal and likely results from migration of EAC epithelium into middle ear via defects in tympanic membrane
 - May lead to destructive keratin-producing tumors known as cholesteatomas

Chronic Injury to Tympanic Membrane

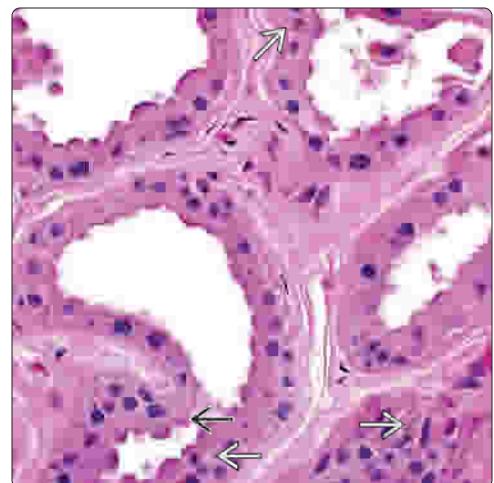
- Usually from chronic otitis media; can lead to sclerosis and secondary dystrophic calcification known as tympanosclerosis

Graphic of Ear Anatomy

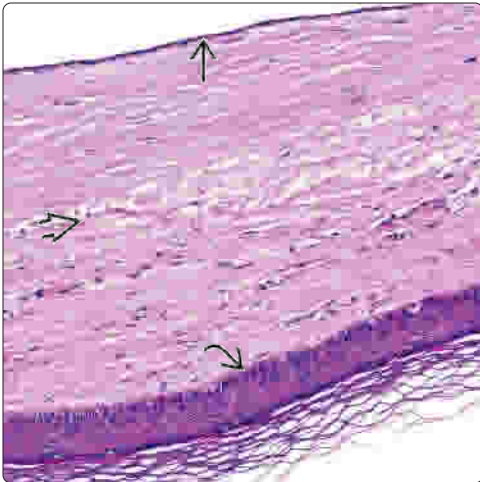


(Left) The external ear auricular cartilaginous framework  is in continuity with the external auditory canal at the concha. The outer 1/3 is supported by cartilage , and the inner 2/3 is supported by bone . (Right) Ceruminous glands are modified apocrine glands characterized by cells with abundant granular eosinophilic cytoplasm, apical snouts , apocrine-type secretion, and yellow cytoplasmic granules .

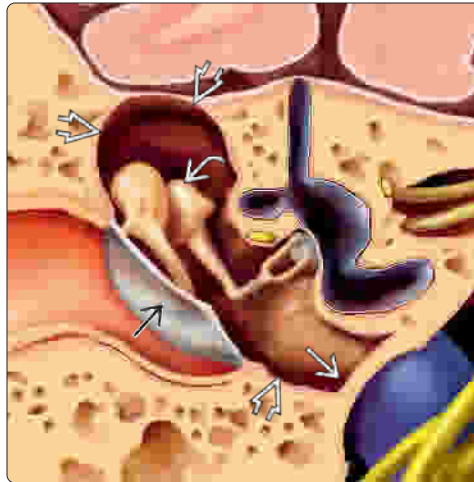
Histology of Ceruminous Glands



Tympanic Membrane Histology

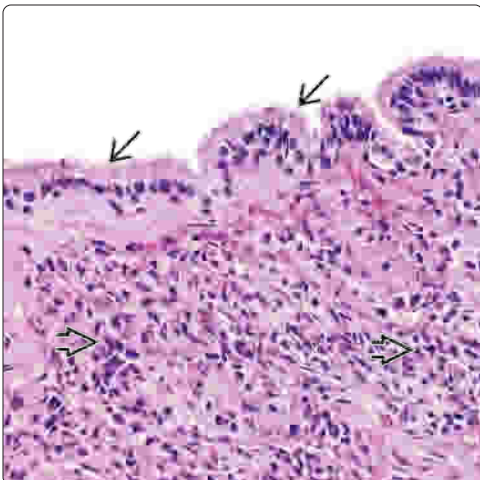


Graphic of Middle Ear Anatomy

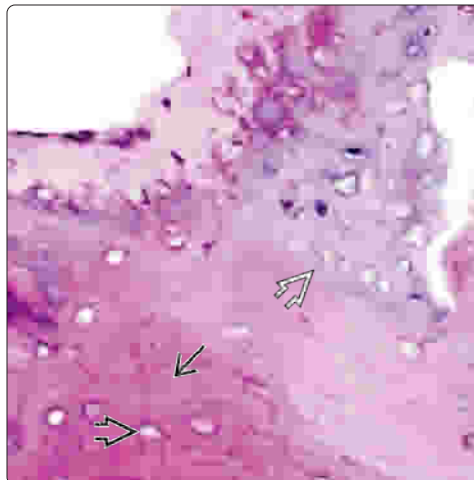


(Left) The tympanic membrane has a thin connective tissue plate lined externally by squamous epithelium devoid of adnexal structures, and internally by modified respiratory epithelium. This tympanic membrane is thickened due to chronic irritation. (Right) The tympanic cavity contains 3 ossicles (lateral to medial: Malleus, incus, stapes), delimited laterally by the tympanic membrane. The tympanic cavity continues as the internal auditory canal (eustachian tube), extending into the nasopharynx.

Histology of Tympanic Cavity

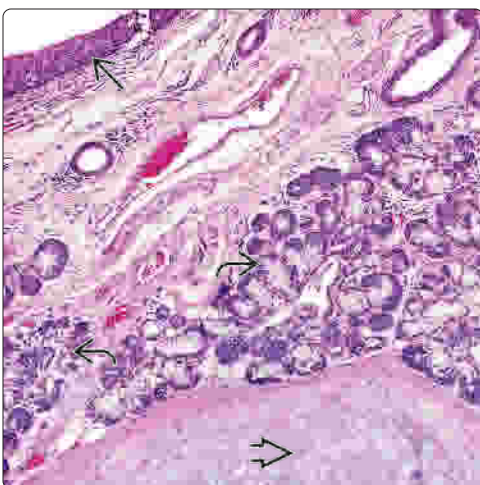


Histology of Ossicles



(Left) While normally lined by cuboidal respiratory-type epithelium, patches of columnar respiratory epithelium complete with cilia are present to varying degrees lining this jugulotympanic paraganglioma. (Right) The ossicles predominantly consist of compact lamellar bone with osteocytes set within lacunae as well as varying numbers of haversian systems. Islands of cartilage can be seen at the periphery of most ossicles.

Histology of Internal Auditory Canal



Histology of Endolymphatic Sac



(Left) The internal auditory canal is lined by respiratory-type epithelium. It is present within bone proximally, but a hyaline cartilage tube supports it distally. Submucosal seromucous glands are present in the distal 2/3 (cartilaginous portion). (Right) While not typically seen as a surgical specimen, portions of the endolymphatic sac can be seen in tumor resection specimens. These appear as epithelial-lined cystic spaces embedded within loose connective tissue or bone.

Accessory Tragus

KEY FACTS

TERMINOLOGY

- Developmental anomaly resulting in presence of lesion recapitulating normal external ear

ETIOLOGY/PATHOGENESIS

- Thought to be 2nd branchial arch anomaly
- May occur with cleft palate or lip, mandibular hypoplasia, or other anomalies, such as OAV dysplasia (Goldenhar syndrome)
- May also occur independent of other congenital anomalies

CLINICAL ISSUES

- Simple surgical excision is curative

MICROSCOPIC

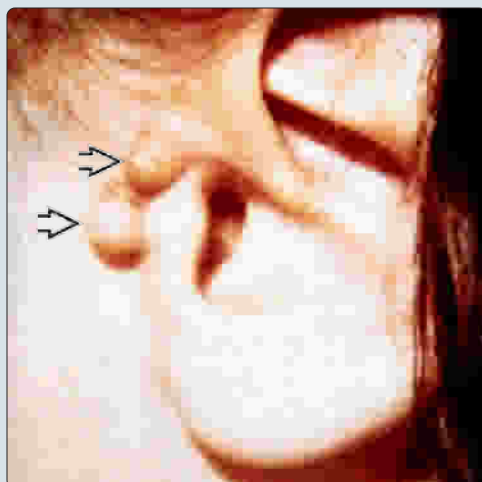
- Recapitulation of normal external auricle
 - Includes skin, cutaneous adnexal structures, and central core of cartilage

TOP DIFFERENTIAL DIAGNOSES

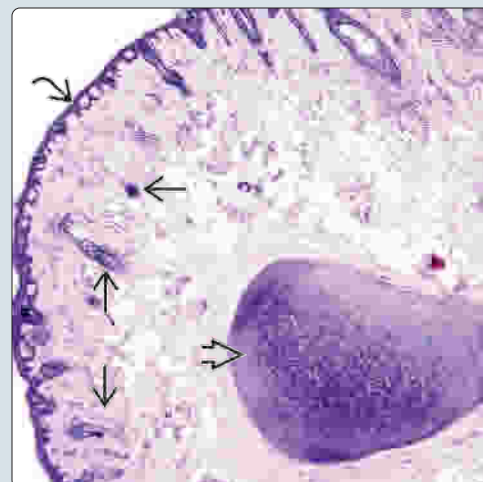
- Squamous papilloma
 - Exophytic proliferation of benign squamous epithelium with fibrovascular cores
 - Lacks cutaneous adnexa and cartilage
- Teratoma
 - Neoplasm characterized by tissue elements of all 3 germ layers including
 - Ectoderm
 - Cutaneous epithelium
 - Central and peripheral nervous system
 - Endoderm may include
 - Columnar epithelium
 - Ciliated respiratory epithelium
 - Gastrointestinal epithelia, including glands
 - Mesoderm
 - Cartilage, bone, adipose tissue, muscle

Accessory Tragi

(Left) Accessory tragi appearing as pedunculated, skin-covered papules located on the skin surface anterior to the auricle. (Right) The histology of accessory tragi recapitulates that of the normal external auricle, including the presence of skin (squamous epithelium), subcutaneous adnexal structures, and central core of cartilage.



Accessory Tragus

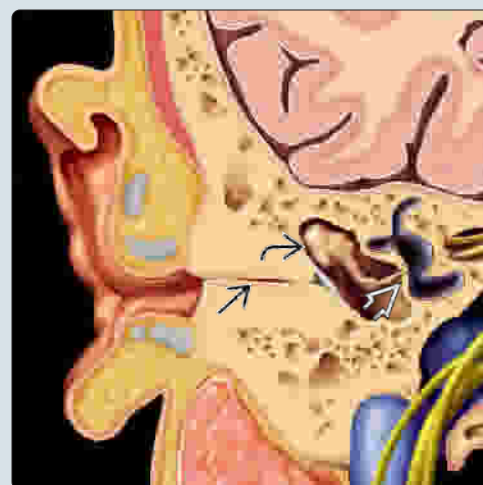


Accessory Tragus

(Left) The diagnostic features of accessory tragi that differentiate it from squamous papilloma include the presence of cutaneous adnexal structures (sebaceous glands, hair follicles, and cartilage). These structures are not present in squamous papillomas. (Right) Coronal graphic of the right ear shows deformed auricle with absent external auditory canal, ossicular fusion mass, and rotation with oval window atresia.



Schematic Representation of Goldenhar Syndrome



TERMINOLOGY**Synonyms**

- Supernumerary ears
- Accessory auricle
- Polyotia

Definitions

- Developmental anomaly resulting in presence of lesion recapitulating normal external ear

ETIOLOGY/PATHOGENESIS**Developmental Anomaly**

- Thought to be 2nd branchial arch anomaly
 - May occur with other anomalies including
 - Cleft palate
 - Cleft lip
 - Mandibular hypoplasia
 - May occur in association with Goldenhar syndrome
 - a.k.a. oculo-auriculo-vertebral (OAV) syndrome
 - Term used interchangeably with hemifacial microsomia
 - Rare congenital defect
 - Characterized by incomplete development of ear, nose, soft palate, lip, mandible
 - Associated with anomalous development of 1st branchial arch and 2nd branchial arch
 - May also occur independent of other congenital anomalies

CLINICAL ISSUES**Epidemiology**

- Age
 - Neonates
- Sex
 - Equal gender distribution

Site

- On skin surface, often anterior to auricle
- Unilateral or bilateral

Presentation

- Skin-covered nodules or papules

Treatment

- Surgical approaches
 - Simple surgical excision is curative

MACROSCOPIC**General Features**

- Nodules or papules
 - Sessile or pedunculated
 - Soft or cartilaginous

MICROSCOPIC**Histologic Features**

- Recapitulation of normal external auricle
- Includes
 - Skin

- Cutaneous adnexal structures
- Central core of cartilage

DIFFERENTIAL DIAGNOSIS**Squamous Papilloma**

- Benign tumor of squamous epithelium
- Exophytic proliferation of benign squamous epithelium with fibrovascular cores
- Lacks cutaneous adnexa and cartilage

Teratoma

- Neoplasm characterized by tissue elements of all 3 germ layers including
 - Ectoderm
 - Cutaneous epithelium
 - Central and peripheral nervous system
 - Others
 - Endoderm may include
 - Columnar epithelium
 - Ciliated respiratory epithelium
 - Gastrointestinal epithelia, including glands
 - Mesoderm
 - Cartilage
 - Bone
 - Adipose tissue
 - Muscle
 - Others

DIAGNOSTIC CHECKLIST**Pathologic Interpretation Pearls**

- Recapitulation of normal external auricle including
 - Skin
 - Cutaneous adnexal structures
 - Central core of cartilage
- In contrast to teratoma, lacks tissue elements of all 3 germ layers

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Encephalocele

KEY FACTS

TERMINOLOGY

- Encephalocele represents herniation of brain tissue and leptomeninges through bony defect

ETIOLOGY/PATHOGENESIS

- Defect in cranial bones or failure of cranial sutures to close
- Surgery, trauma, postinfectious/inflammatory may result in encephalocele formation

CLINICAL ISSUES

- Nonmidline: Middle ear, mastoid bone, orbit, scalp, neck soft tissues
- Midline: Nasal cavity, nasopharynx, palate, tongue
- Ear lesions frequently associated with chronic otitis media &/or mastoiditis
- Nasal lesions frequently associated with rhinorrhea, obstruction, or difficulty breathing
- At surgery, CNS leak or bony abnormality documented to prove CNS connection

IMAGING

- Must be done to identify relationship to CNS

MICROSCOPIC

- Glial heterotopia indistinguishable pathologically from encephalocele
- Variable proportions of neurons and glia
- Associated reactive gliosis
- Chronic inflammatory cells (lymphocytes and macrophages) present in nearly all cases
- Leptomeninges, ependyma, and choroid plexus nearly always **absent**

ANCILLARY TESTS

- **Positive:** GFAP and S100 protein in glial tissue; NFP in neuronal tissue

TOP DIFFERENTIAL DIAGNOSES

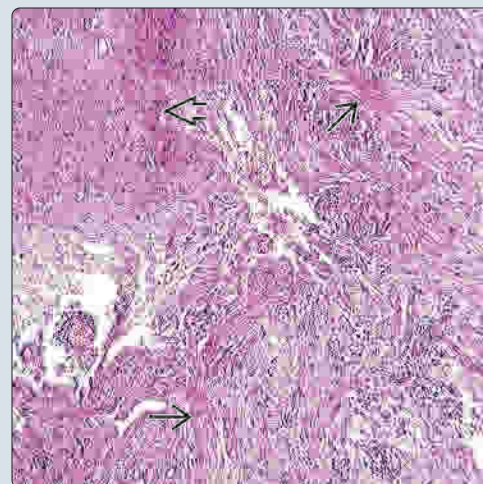
- Teratoma, glioma, meningioma, schwannoma

CT of Middle Ear Encephalocele

(Left) A temporal bone CT reveals a pedunculated encephalocele hanging through a focal dehiscence of tegmen tympani. This developed as a postoperative complication. (Right) This encephalocele shows fibrosis and intermixed gliosis. Inflammatory cells are sparse. Ear encephaloceles often have associated otitis media.

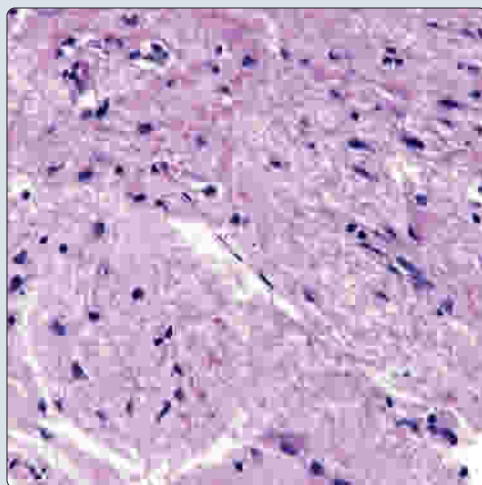


Gliosis in Encephalocele

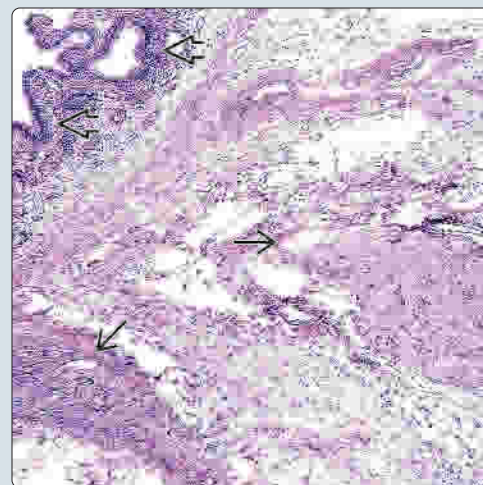


Fibrillar Neural Matrix and Reactive Fibroblasts

(Left) Hematoxylin and eosin shows the fibrillar neural matrix material and reactive fibroblasts. This appearance can sometimes mimic fibrosis. Careful evaluation shows the neural nature of the lesion. (Right) A nasal cavity encephalocele demonstrates respiratory mucosa and shows fibrosis surrounding gliotic neural tissue. Glial heterotopia would be in the differential diagnosis.



Respiratory Mucosa in Encephalocele of Nasal Cavity



TERMINOLOGY

Synonyms

- Neuroglial heterotopia, extracranial glioma, glial choristomas, hamartoma, monodermal teratoma

Definitions

- Encephalocele represents herniation of brain tissue and leptomeninges through bony defect of skull, maintaining continuity with cranial cavity
- Heterotopic neuroglial tissue defined as mass of mature brain tissue isolated from cranial cavity or spinal canal

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Defect in cranial bones or failure of cranial sutures to close
 - Related to glial heterotopia if CNS connection resorbed

Iatrogenic or Acquired

- Surgery, trauma, postinfectious/inflammatory may result in encephalocele formation
- Most nonmidline lesions interpreted to be acquired

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon; increased in postsurgical, traumatic, and infectious setting
- Age
 - Anatomic site of development associated with age
 - Nonmidline lesions: Older patients (mean: 50 years)
 - Midline lesions: Young age (< 2 years)

Site

- Nonmidline: Middle ear, mastoid bone, orbit, scalp, neck
- Midline: Nasal cavity, nasopharynx, palate, tongue

Presentation

- Depends on anatomic site of involvement
- Ear lesions frequently associated with chronic otitis media &/or mastoiditis
 - Deafness, hearing loss, dizziness, tympanic membrane perforation, cerebrospinal fluid (CSF) otorrhea
- Nasal lesions frequently associated with rhinorrhea, obstruction, or difficulty breathing
- Previous surgery or trauma identified in many (especially older patients)

Laboratory Tests

- Test fluid for glucose and protein to exclude CSF

Treatment

- At surgery, CNS leak or bony abnormality documented to prove CNS connection
- Clinician and pathologist must communicate about exact location and relationship to dura or nerves

Prognosis

- Excellent outcome with surgery alone; CNS connection must be documented to preclude postoperative CNS leak, infection, and herniation

IMAGING

Radiographic Findings

- Must be done to identify relationship to CNS
- Even if negative, CNS connection frequently identified at surgery

MICROSCOPIC

Histologic Features

- Glial heterotopia indistinguishable pathologically from encephalocele
- Variable proportions of neurons and glia
- Associated reactive gliosis
- Chronic inflammatory cells (lymphocytes and macrophages) present in nearly all cases
 - Encephalocele may be seen with otitis media
- Leptomeninges, ependyma, and choroid plexus nearly always absent
- Isolated glandular elements (apocrine, mucoserous glands native to regions), skin, and bone may be identified entrapped by process
- Keratin debris from concurrent cholesteatoma in middle ear lesions can be seen
- Tympanic membrane or eustachian tube epithelium must not be mistaken for teratomatous elements

ANCILLARY TESTS

Histochemistry

- Masson trichrome stains glial tissue red and collagen/fibrosis blue

Immunohistochemistry

- **Positive:** GFAP and S100 protein in glial tissue; neurofilament protein in neuronal tissue
- **Negative:** Keratin

DIFFERENTIAL DIAGNOSIS

Teratoma

- Mature glial tissue may predominate, but tissue from all 3 germ cell primordia should be identified

Glioma

- Neoplastic proliferation with ↑ cellularity, disorganized growth, usually without fibrosis or inflammatory cells

Meningioma

- Epithelioid cells showing whorled and syncytial architecture, possible psammoma bodies, EMA(+)

Schwannoma

- Antoni A and B areas, spindle cell proliferation, elongated nuclei, palisading

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First Branchial Cleft Anomaly

KEY FACTS

TERMINOLOGY

- Spectrum of benign, congenital lesions occurring in parotid, posterior submandibular space, or preauricular region as fistula, sinus, or cyst
 - Results from incomplete fusion of 1st and 2nd branchial arches, with persistence of ventral component of 1st branchial cleft

CLINICAL ISSUES

- < 10% of all branchial cleft anomalies
- Most discovered in early childhood (< 10 years)
- Recurrent, preauricular or periparotid swelling
- Draining sinus tract on periauricular skin (type II)
 - Chronic, unexplained otorrhea or purulent drainage from ear canal
- Complete excision of lesion(s); use antibiotic treatment prior to surgery (if infected)

IMAGING

- Cystic mass around pinna (type I) or extending from external auditory canal (EAC) to angle of mandible (type II: Using Arnot criteria)

MICROSCOPIC

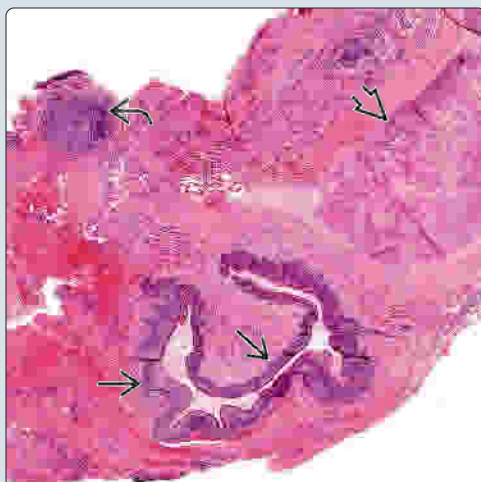
- Cyst, sinus, or fistula lined by stratified squamous or ciliated respiratory epithelium
- Separated into 2 **histologic** types by Work
 - Type I: Epithelium only
 - Type II: Epithelium with cutaneous adnexal structures &/or cartilage

TOP DIFFERENTIAL DIAGNOSES

- Epidermal inclusion cyst, benign lymphoepithelial cyst, chondrocutaneous vestige, folliculitis/abscess, metastatic cystic squamous cell carcinoma, mucoepidermoid carcinoma

Fistula With Cartilage

(Left) A fistula is lined by a keratinizing squamous lining, and cartilage is identified in the immediately associated tissue. Note the blind ending of the fistula. **(Right)** The fistula or sinus is lined by either keratinizing squamous epithelium (as in this case) or by respiratory type epithelium. The presence of cartilage helps to confirm a Work type II lesion. There is no inflammation in this case.

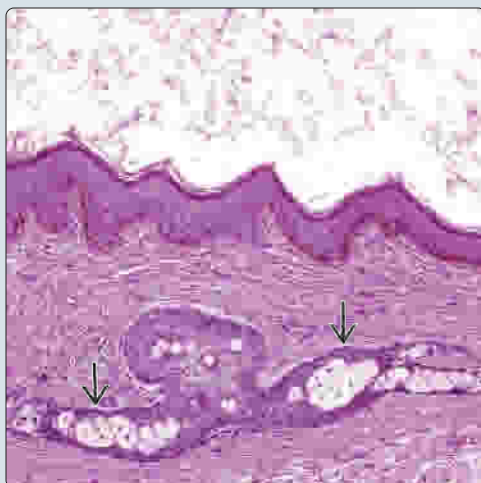


Cartilage Adjacent to Squamous Cyst

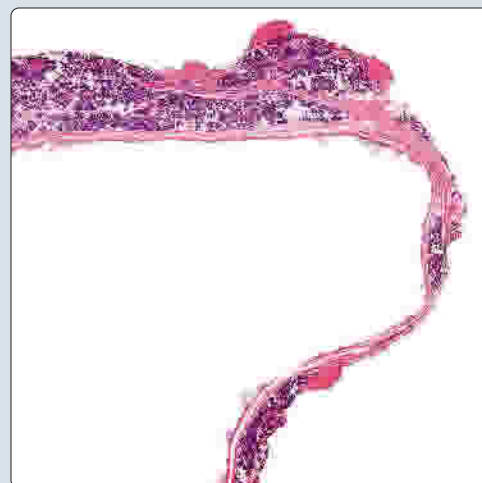


Cyst With Adnexal Structures

(Left) There is keratin debris within the lumen of this squamous-lined cyst. Within the wall of the cyst, isolated skin adnexal structures are identified focally with sebaceous differentiation. This is a Work type II lesion. **(Right)** There is a cystic space within the superficial lobe of the parotid gland in a patient with a fistula extending to the external auditory canal (EAC). Histologically this could mimic a primary salivary gland lesion.



Intraparotid Gland Cyst



TERMINOLOGY

Abbreviations

- 1st branchial cleft cyst (BrCC)

Synonyms

- Cervicoaural cyst
- 1st branchial apparatus remnant

Definitions

- Spectrum of benign, congenital lesions occurring in parotid, posterior submandibular space, or preauricular region as fistula, sinus, or cyst
 - Results from incomplete fusion of 1st and 2nd branchial arches, with persistence of ventral component of 1st branchial cleft

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Persistence of 1st branchial apparatus
 - 1st branchial **cleft** gives rise to external auditory canal (EAC)
 - 1st branchial **arch** gives rise to mandible, muscles of mastication, CN V, incus body, and head of malleus
 - 1st branchial **pouch** gives rise to eustachian tube, middle ear cavity, and mastoid air cells
- BrCC has no internal (pharyngeal) or external (cutaneous) communication (blind pouch)
- Branchial cleft fistula has internal and external connections from EAC to skin
- Branchial cleft sinus opens either internally (rare) or externally, with closed-end blind pouch

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon
 - < 10% of all branchial cleft anomalies
 - ~ 2/3 of 1st branchial cleft remnants present as fistulas and sinuses rather than cysts
 - Type II > Type I
 - Periauricular with sinuses/fistulas in anterolateral neck or external auditory canal
- Age
 - Most discovered in early childhood (< 10 years)
 - Type I anomalies usually seen in adults
 - Type II anomalies usually < 1 year of age
- Sex
 - Female > male (2:1)

Site

- Periauricular: Preauricular and immediately postauricular, frequently involving parotid gland
- **Not** associated with **pretragal** cysts, pits, or sinuses

Presentation

- Recurrent, painless, soft, compressible cyst or mass in preauricular or periparotid area
- Majority present as sinus or fistula rather than cyst
- Draining sinus tract on periauricular skin (type II)

- Chronic, unexplained otorrhea or purulent drainage from ear canal
- May have recurrent parotid gland abscess
- Rare syndrome association: Branchiootorenal syndrome (Melnick-Fraser syndrome)

Natural History

- May wax and wane with upper respiratory tract infection
- May undergo repeat incision and drainage, with recurrence

Treatment

- Surgical approaches
 - Complete excision of lesion(s) (cyst, sinus, &/or fistula); use antibiotic treatment prior to surgery (if infected)
 - Easily dissected, except if there has been repeated infection
 - Must include termination of pouch at EAC between cartilaginous and bony portions
 - Type II: May split facial nerve trunk, with medial or lateral placement of CN VII
- Recurrence if incompletely resected
- Facial nerve may be at risk during surgery

Prognosis

- Secondary infection of cyst, sinus, or fistula
- Facial nerve injury must be avoided
- Recurrences if incompletely excised, or managed with incision and drainage procedures
- No malignant potential

IMAGING

General Features

- Best study is contrast-enhanced CT (high resolution) or MR
- Cystic mass around pinna (type I) or extending from EAC to angle of mandible (type II)
- Well-circumscribed, unilocular ovoid cyst
- Separated into **anatomic** sites based on Arnot
- Type I: Periauricular (less common); anterior, below or posterior to pinna (but most commonly preauricular)
- Type II: Periparotid (most common); superficial parotid and parapharyngeal spaces

CT Findings

- Well-circumscribed, nonenhancing or rim-enhancing, low-density mass
- Type I: Lesion may beak toward bony-cartilaginous junction of EAC
- Type II: Superficial, parotid, or parapharyngeal space with deep projection beaking to bony-cartilaginous junction of EAC

MACROSCOPIC

General Features

- Discrete cysts, sinuses, or fistulas, or combination of these structures
- Cyst contents: Viscous, cloudy fluid to purulent and necrotic material (pus when infected)
- Cartilage may be identified
- Sinus tract extending from external auditory canal or periauricular skin

Size

- Variable; up to 4 cm

MICROSCOPIC

Histologic Features

- Cyst, sinus, or fistula lined by stratified squamous or ciliated respiratory epithelium
- Separated into 2 **histologic** types by Work
 - Type I
 - Usually cyst rather than sinus or fistula
 - Epithelium only, lined by either stratified squamous epithelium or ciliated respiratory epithelium
 - Type II
 - Cyst with sinus or fistula between neck and ear canal
 - Lined by either stratified squamous epithelium or ciliated respiratory epithelium
 - Contains **cutaneous adnexal structures &/or cartilage** (mesodermal component)
 - May need to do serial sections or deeper levels to identify cartilage or adnexal tissue
- Cyst wall may contain lymphoid aggregates, sometimes with germinal centers
- If infected, epithelium is largely denuded, replaced by heavily inflamed granulation tissue

ANCILLARY TESTS

Cytology

- Fine-needle aspiration is recommended in evaluation of all neck cysts
 - Usually of residual cyst post antibiotic therapy
- Thick, yellow, pus-like material is aspirated
- Smears are generally cellular
- Comprised of anucleate squames and mature squamous epithelium
 - Columnar respiratory type cells are less common
- Amorphous debris often associated with macrophages
- Lymphoid infiltrate, including plasma cells
- Adnexal structures usually not aspirated

Immunohistochemistry

- p16(-)

DIFFERENTIAL DIAGNOSIS

Epidermal Inclusion Cyst

- Cyst containing keratin debris and lined by squamous epithelium
- Impossible to separate without clinical information, including exclusion of sinus or fistula

Benign Lymphoepithelial Cyst

- Intimate blending of epithelium with lymphoid tissue, but lacks sinus/fistula
- Parotid gland involvement primarily: HIV-associated if bilateral

Folliculitis/Abscess

- Superficial dermis-based, centered on hair or follicle structures, lacking sinus, fistula, or cyst

Chondrocutaneous Vestige (Choristoma)

- Identified at birth, originating from 1st or 2nd arch, frequently associated with fetal malformations or anomalies
- Presents in lower 1/3 of neck, usually at anterior border of sternocleidomastoid muscle
- Central cartilaginous core with cutaneous/subcutaneous tissue envelope (no cyst)

Metastatic Cystic Squamous Cell Carcinoma

- Jugulodigastric lymph node most commonly affected
- Unilocular cyst with very thick, well-developed capsule, showing subcapsular sinus and medullary zone
- Ribbon-like distribution of atypical epithelium, lacking maturation, often with limited pleomorphism and mitoses
- Primary tumor usually identified in Waldeyer ring (oropharynx)
 - Often nonkeratinizing and p16(+)
- Primary branchiogenic carcinoma does **not** exist

Mucoepidermoid Carcinoma

- Multicystic malignancy of salivary gland (parotid in this setting)
- Epidermoid, transitional, and mucocytes blended together
- Invasion frequently present (capsule, vessel, nerve)
- Cytologic atypia usually easy to identify, although, it does not have to be extensive, with mitoses

STAGING

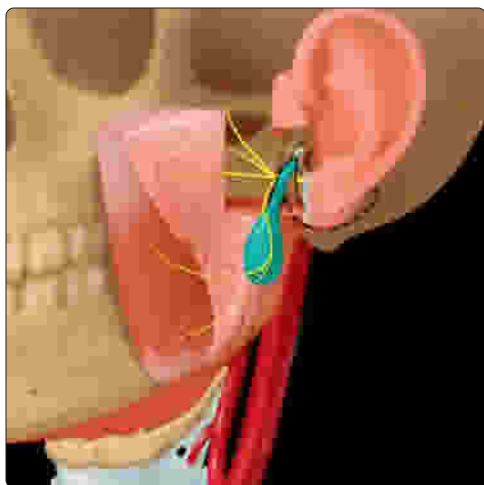
Annot (Anatomic)

- Type I: Cyst or sinus in parotid gland; adulthood
- Type II: Cyst or sinus in anterior cervical triangle communicating with EAC; childhood

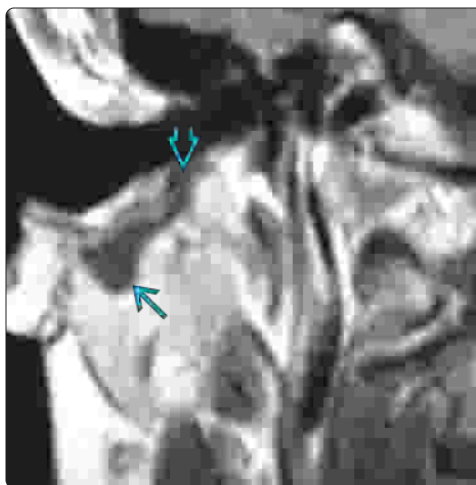
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
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Graphic of Anatomy and Cyst Formation



MR of Type I Branchial Cleft Cyst (BrCC)





(Left) Graphic shows the intimate association with the facial nerve (yellow) and the parotid gland with a 1st BrCC. The tract of a sinus or fistula involves the EAC and can continue to the hyoid bone or show a retroauricular extension (dotted lines). (Right) Coronal T1WI MR with contrast shows a type I BrCC  immediately below and parallel to the EAC and superficial to CN VII, with a tract to the EAC at the confluence of the cartilaginous and bony portions . This is a characteristic finding.

Intraoperative Photograph of 1st BrCC

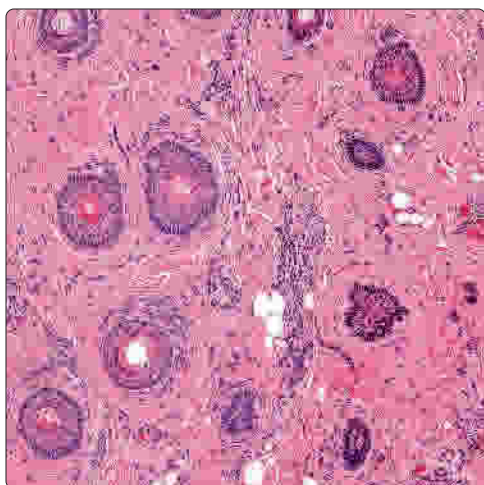


Squamous-Lined Cyst With Cartilage

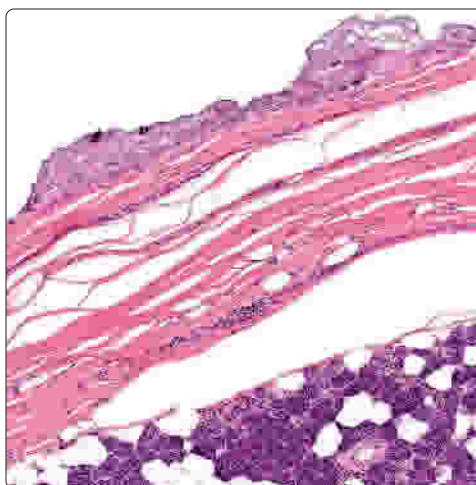


(Left) There is a well-developed cystic cavity identified just anterior to the ear and below the skin. Cartilage was present in this lesion histologically and diagnosed as a Work type II lesion. (Right) There is a squamous epithelial-lined cyst  as part of this branchial cleft anomaly. The presence of cartilage  helps to confirm a Work type II formation.

Hair Shafts and Follicular Structures



Parotid Gland Location of BrCC



(Left) The presence of skin adnexal structures in the form of hair shafts, follicular structures, or pilosebaceous units are frequently identified within the cyst wall or immediately adjacent to it in a Work type II anomaly. (Right) The parotid gland tissue is separated from the cyst by a capsule. The predominantly keratinized squamous epithelium is partially disrupted. There is no inflammation. These findings may mimic primary salivary gland cysts.

Otitis Media

KEY FACTS

TERMINOLOGY

- Acute or chronic infectious disease of middle ear space
 - AOM: Viral or bacterial infection of middle ear
 - COM: Persistent infection or inflammation of middle ear

ETIOLOGY/PATHOGENESIS

- Most common organisms implicated in causing disease are *Streptococcus pneumoniae* and *Haemophilus influenzae*

CLINICAL ISSUES

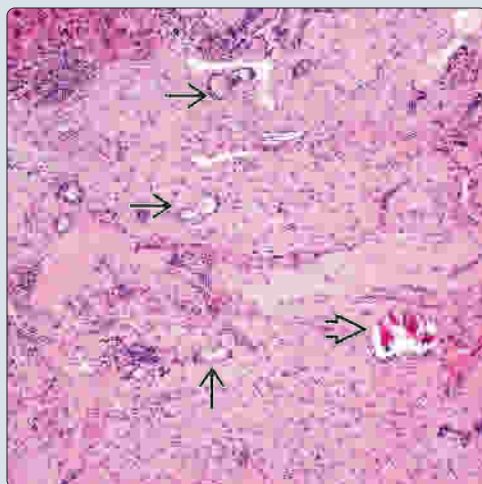
- High incidence: 30-35 million cases/year
- May occur at any age but predominantly childhood disease particularly common in children under 3 years of age
- Symptoms are frequently nonspecific
 - Fever, irritability, pulling ears, headache, cough, rhinitis, listlessness, anorexia, vomiting, diarrhea
 - Decreased hearing
- 70-90% of AOMs resolve spontaneously within 14 days

- Wide variety used, but amoxicillin used most frequently (specific exclusions apply)

MICROSCOPIC

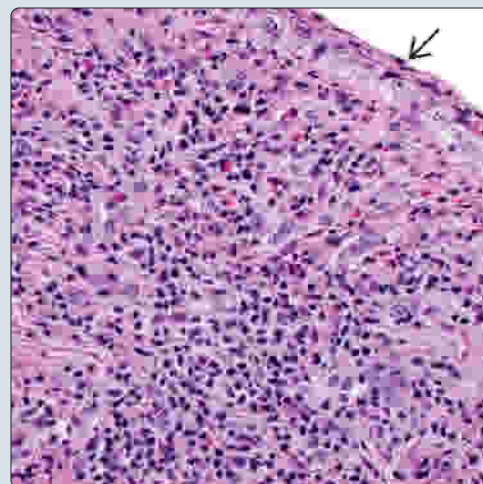
- Chronic otitis media histologic changes include
 - Variable amount of chronic inflammatory cells consisting of lymphocytes, histiocytes, plasma cells and eosinophils
 - Multinucleated giant cells and foamy histiocytes may be present
 - Glandular metaplasia
 - Glands are variably shaped and are separated by abundant stromal tissue
 - Glands are lined by columnar to cuboidal epithelium ± cilia or goblet cell metaplasia
 - Tympanosclerosis
 - Represents dystrophic mineralization (calcification or ossification) of tympanic membrane or middle ear; incidence varies from 3-33%
 - Cholesterol granuloma formation

Histology of Chronic Otitis Media



(Left) Low-magnification histologic changes associated with chronic otitis media include fibrosis, chronic inflammation, glandular metaplasia [X], and tympanosclerosis [X]. The glands are widely spaced in contrast to the diffuse proliferation in neuroendocrine adenoma of middle ear. (Right) In chronic otitis media, the low cuboidal epithelium [X] of the middle ear may be present subtended by a chronic inflammatory cell infiltrate composed of an admixture of lymphocytes, plasma cells, and eosinophils.

Histology of Chronic Otitis Media



CT Findings of Acute Otitis Media



(Left) Axial bone CT shows complete opacification of the middle ear-mastoid, along with focal loss of the short process of the incus [X]. The loss of incus bony integrity indicates that acute infection is present. (Right) Clinical features that may occur in acute otitis media include a hyperemic, opaque, bulging tympanic membrane [X] and the infectious accumulation of purulent fluid [X] within the middle ear resulting in decreased hearing.

Graphic Depiction of Acute Otitis Media



TERMINOLOGY

Definitions

- Acute or chronic infectious disease of middle ear space
 - Acute otitis media (AOM): Viral or bacterial infection of middle ear
 - Chronic otitis media (COM): Persistent infection or inflammation of middle ear and mastoid air cells

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Most common organisms implicated in causing disease are *Streptococcus pneumoniae* and *Haemophilus influenzae*

CLINICAL ISSUES

Epidemiology

- Incidence
 - High: 30-35 million cases/year
 - 3% of all patient visits
- Age
 - May occur at any age but predominantly childhood disease particularly common in children under 3 years of age
 - Peak: 6-12 months
 - ◻ Lower peak: 4-5 years
 - ◻ ~60% of children < 1 year old will have had AOM
 - Adults: < 20% of all AOM patients

Site

- Middle ear by definition
 - Tympanic membrane (TM) perforation may develop, extending into external auditory canal (EAC)

Presentation

- Symptoms are frequently nonspecific
 - Fever, irritability, pulling ears, headache, cough, rhinitis, listlessness, anorexia, vomiting, diarrhea
 - Decreased hearing
 - Symptoms typically preceded by several days of upper respiratory tract infection
- Otoscopic examination reveals a hyperemic, opaque, bulging tympanic membrane with limited mobility
 - Purulent otorrhea may be present
- COM: Persistent or recurrent otorrhea through perforated tympanic membrane, thickened granular mucosa, cholesteatoma
- Adults: Present with otalgia, ear drainage, decreased acuity, sore throat, decreased hearing

Treatment

- Options, risks, complications
 - 70-90% of AOMs resolve spontaneously within 14 days
 - Potential complications: TM perforation, otitis externa, mastoiditis, labyrinthitis, meningitis, vestibular dysfunction
 - In antibiotic era, complications associated with otitis media are not generally seen; however, if left unchecked, complications of otitis media occur, which can be divided into
 - Intratemporal complications

- ◻ Mastoiditis, petrositis, labyrinthitis and facial nerve paralysis
- Intracranial complication
 - ◻ Meningitis, lateral sinus thrombophlebitis and brain abscess
- In adults, unresolving otitis media should warrant detailed examination of nasopharynx in order to rule out presence of (malignant) neoplasm (i.e., nasopharyngeal carcinoma)
- Surgical approaches
 - Rarely a surgically treated disease
 - Tympanocentesis and culture in limited circumstances
 - Toxic patient, failed multiple courses of antibiotics, immune deficient
 - Myringotomy ± ventilation tubes
 - Adenoidectomy
- Drugs
 - Wide variety used, but amoxicillin used most frequently (specific exclusions apply)

MICROSCOPIC

Histologic Features

- Acute otitis media
 - Virtually never surgical disease
- Chronic otitis media histologic changes include
 - Variable amount of chronic inflammatory cells consisting of lymphocytes, histiocytes, plasma cells, and eosinophils
 - Multinucleated giant cells and foamy histiocytes may be present
 - Glandular metaplasia
 - Glands are variably shaped and are separated by abundant stromal tissue
 - Glands are lined by columnar to cuboidal epithelium ± cilia or goblet cell metaplasia
 - Tympanosclerosis
 - Represents dystrophic mineralization of tympanic membrane or middle ear (incidence: 3-33%)
 - Cholesterol granuloma formation

DIFFERENTIAL DIAGNOSIS

Middle Ear Adenoma ± Neuroendocrine Differentiation

- Histology dominated by presence of diffuse glandular &/or solid cell proliferation rather than haphazard arrangement of glands in COM

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KEY FACTS

TERMINOLOGY

- Virulent and potentially fatal form of external otitis related to *Pseudomonas aeruginosa* infection

ETIOLOGY/PATHOGENESIS

- External otitis related to *Pseudomonas aeruginosa* infection
 - Felt to be caused by tissue ischemia secondary to underlying predisposing pathologic state (e.g., diabetic angiopathy) and migratory defect of polymorphonuclear leukocytes related to systemic disease
 - These host factors impede inflammatory response to infection and, combined with destructive devices of *P. aeruginosa*, are thought to be responsible for lethal potential of necrotizing external otitis

CLINICAL ISSUES

- Primarily affects older patients
- Diabetic, chronically debilitated, or immunologically deficient patients; may occur in nondebilitated patients

- Surgical debridement
- Combination therapy with intravenous ceftazidime and oral fluoroquinolone
- Mortality rates > 75% if diagnosis and treatment delayed
- Cure can be achieved with early recognition and aggressive treatment

MICROSCOPIC

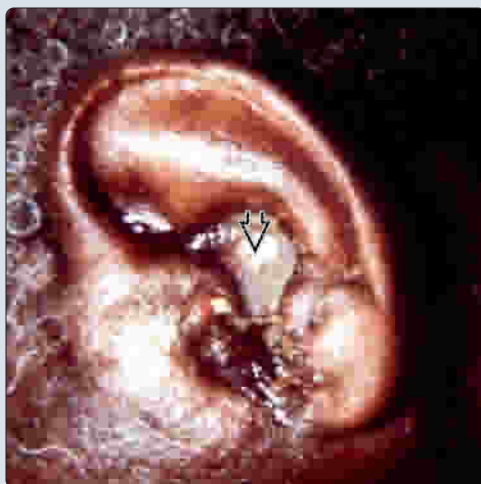
- Histology dominated by presence of necrotic material and exuberant granulation tissue
- Necrotizing vasculitis commonly present
- Diffuse heavy acute and chronic inflammation present in subcutis
- Thick, acellular collagen replaces dermis extending from cartilage to overlying dermis
- Necrosis of bone and cartilage with inflammatory cells infiltrating adjacent viable bone

ANCILLARY TESTS

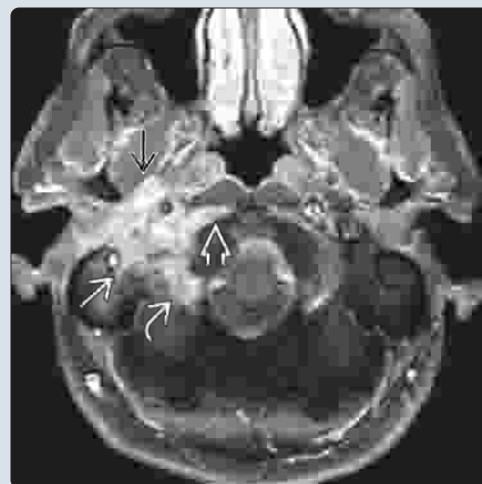
- Presence of gram-negative bacilli readily identified

Clinical Presentation of NEO

(Left) The clinical features that can be seen in association with NEO include a swollen ear with necrotic exudate seen within the external auditory canal (EAC) [red box] (purulent otorrhea). The patient had a history of longstanding diabetes complaining of progressive increasing ear-related pain. (Right) Axial T1 C+ FS MR shows enhancing tissue extending from right EAC into parapharyngeal space [red box], prevertebral space [red box], occipital bone [red box], and stylomastoid foramen [red box] in a patient with necrotizing otitis externa.

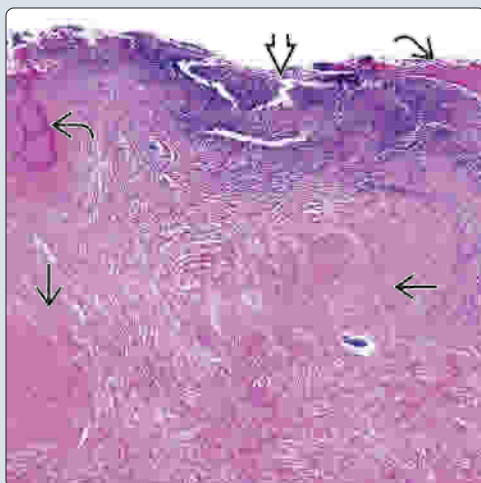


Radiologic Features of NEO

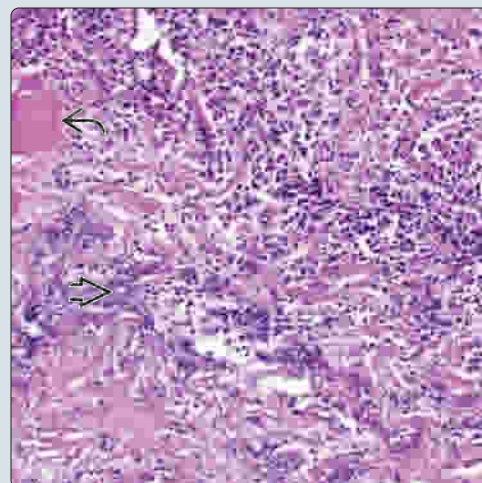


Histology of NEO

(Left) The histologic findings in necrotizing otitis media include epithelial ulceration with associated dense inflammatory cell infiltrate [red box] that extends to bone [red box]. Thick, acellular (keloid-like) collagenous bands replace the subcutis tissues [red box] of the external auditory canal. (Right) Necrosis [red box] and a dense acute and chronic inflammatory cell infiltrate extending to bone [red box] are identified. The histologic findings coupled to the clinical presentation are diagnostic for necrotizing otitis media.



Histology of NEO



TERMINOLOGY**Abbreviations**

- Necrotizing external otitis (NEO)

Synonyms

- Malignant external otitis

Definitions

- Virulent and potentially fatal form of external otitis most frequently related to *Pseudomonas aeruginosa* infection
 - ↑ frequency of fungal (*Aspergillus*, other) and polymicrobial temporal bone infections reported

ETIOLOGY/PATHOGENESIS**Infectious Agents**

- *P. aeruginosa* produces endo- and exotoxins, neurotoxins, collagenases, and elastases, which cause tissue necrosis and necrotizing vasculitis

Pathogenesis

- Felt to be caused by tissue ischemia secondary to underlying predisposing pathologic state (e.g., diabetic angiopathy) and migratory defect of polymorphonuclear leukocytes related to systemic disease
 - These host factors impede inflammatory response to infection and, combined with destructive devices of *P. aeruginosa*, are thought to be responsible for lethal potential of NEO

CLINICAL ISSUES**Epidemiology**

- Age
 - Primarily older patients; rarely occurs in children
- Sex
 - Equal gender distribution

Presentation

- Diabetic, chronically debilitated, or immunologically deficient patients; may occur in nondebilitated patients
- Purulent otorrhea, swelling of ear, acute otitis externa; pain occurs with progression of disease
- Changes most pronounced in osseous portion of external auditory canal (EAC) where destruction begins
 - Skin ulceration leaves layer of thick granulation tissue covering exposed bone
- Fully developed NEO includes abundant necrotic tissue along with purulent exudate, which may obstruct EAC

Laboratory Tests

- Microbiologic cultures
 - *P. aeruginosa* most commonly cultured
 - In culture-negative cases &/or multidrug resistant cases, organisms other than *P. aeruginosa* should be considered

Treatment

- Surgical approaches
 - Surgical debridement
- Drugs
 - Combination therapy with intravenous ceftazidime and oral fluoroquinolone

Prognosis

- Mortality rates > 75% if delay in diagnosis and treatment
- Extensive spread of infection to adjacent structures, including cranial involvement, may result in death
 - Involvement of clivus portends poorer prognosis
- Potentially curable with early recognition and aggressive treatment

IMAGING**General Features**

- CT preferred at initial diagnosis: Destructive osteomyelitis to bony EAC, especially affecting inferior portion

MICROSCOPIC**Histologic Features**

- Histology dominated by presence of necrotic material and exuberant granulation tissue
 - Intact epithelium may show pseudoepitheliomatous hyperplasia &/or atypical features
- Necrotizing vasculitis commonly present
- Diffuse acute and chronic inflammation present
- Thick, acellular collagen replaces dermis extending from cartilage to overlying dermis
- Necrosis of bone and cartilage with inflammatory cells infiltrating adjacent viable bone
- Sequestra of nonviable bone or cartilage may be seen

ANCILLARY TESTS**Histochemistry**

- Presence of gram-negative bacilli readily identified

DIFFERENTIAL DIAGNOSIS**Squamous Cell Carcinoma (SCC)**

- Clinical presentation of SCC of external auditory canal may mimic NEO, or both may occur concurrently
 - Nests of squamous epithelium within dermis with atypical cytologic features
 - Radiographic evidence of destructive process
 - SCC associated with extensive necrosis may elude diagnosis in limited tissue sampling

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Chondrodermatitis Nodularis Helicis

KEY FACTS

TERMINOLOGY

- Nonneoplastic inflammatory and degenerative process of ear characterized by necrobiotic dermal changes
 - Etiologies include local trauma, actinic damage, and tenuous vascularity
- Transepidermal elimination disorder

CLINICAL ISSUES

- Relatively common
- Mean: 6th decade
- Male > female (3:2)
- Mean age at presentation: 6th decade
- Painful, solitary, exquisitely tender nodule on external ear
 - Helix in men; antihelix in women
- Central ulcer or depression with horny plug, often with scale crust
- Needs to be shaved down to underlying cartilage to remove all inflammation

MACROSCOPIC

- Mean: 4-7 mm



MICROSCOPIC

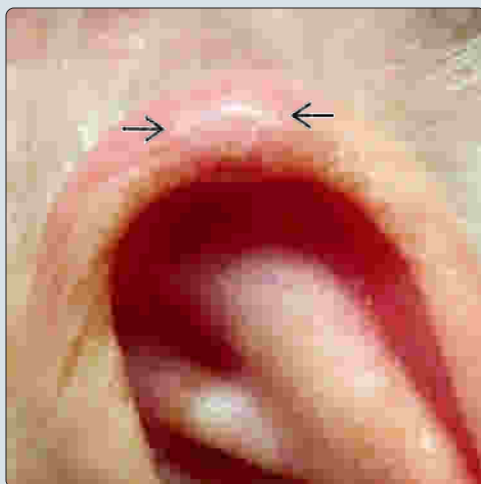
- Epidermal hyperplasia adjacent to keratinaceous (horny) plug
 - Inverted funnel-shaped defect in epidermis
- Upper dermis displays fibrinoid necrosis
- Necrobiotic collagen (collagenolytic destruction)
- Sinus tract created between surface and underlying cartilage

TOP DIFFERENTIAL DIAGNOSES

- Relapsing polychondritis
- Cystic chondromalacia (auricle pseudocyst)
- Squamous cell carcinoma
- Actinic keratosis

Erythematous Nodule on Helix




(Left) There is a raised, erythematous nodule with slight scaling  on the ear helix in a patient with chondrodermatitis nodularis helicis. (Courtesy M. Guralnick, MD.) (Right) The surface is ulcerated with a central, inverted funnel-shaped crater in this example of chondrodermatitis nodularis helicis (CDNH). Note the necrobiosis  of the dermal collagen, down to the cartilage, a characteristic for this transepidermal elimination disorder.

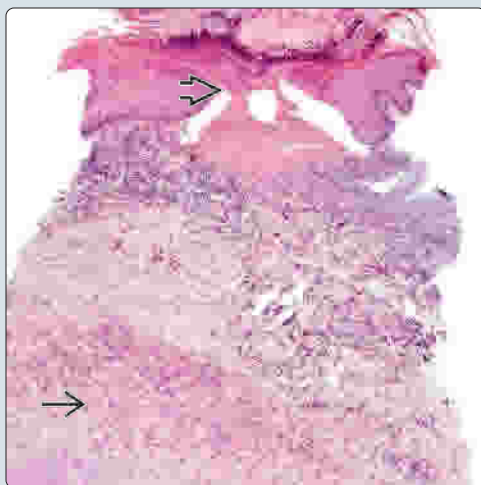


Inverted Funnel-Shaped Ulceration

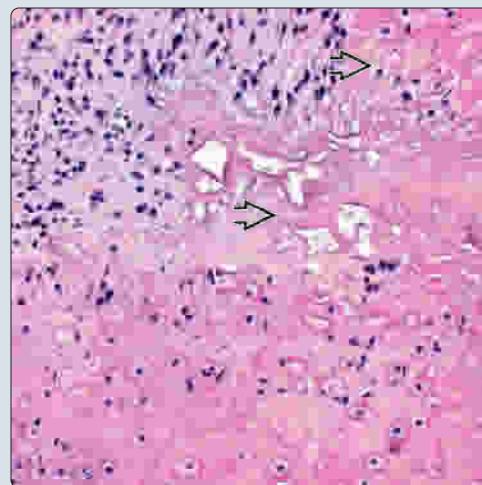


Central Ulcer With Necrobiosis

(Left) Surface crust overlies an area of inverted funnel-shaped ulceration . There is necrobiosis of the collagen, extending down to the perichondrium of the cartilage , along with mixed inflammation and solar elastosis. (Right) The cartilage has some fibrosis and an inflammatory infiltrate with early destruction. There is fibrinoid necrosis  of the dermis.



Fibrinoid Necrosis Extending to Cartilage



TERMINOLOGY

Abbreviations

- Chondrodermatitis nodularis helicis (CDNH)

Synonyms

- Transepithelial elimination disorder; perforating dermatoses; Winkler disease

Definitions

- Nonneoplastic inflammatory and degenerative process of auricle, characterized by necrobiotic changes in dermis that extend down to perichondrium

ETIOLOGY/PATHOGENESIS

Dermal Injury

- Caused by combination of factors: Local trauma, such as rubbing or pressure (prurigo nodularis-like); actinic damage from long-term sun exposure; relatively tenuous vascularity of auricle; cold

Immune-Based

- Linked with granuloma annulare, dermatomyositis, and systemic sclerosis

CLINICAL ISSUES

Epidemiology

- Incidence
 - Relatively common
- Age
 - Mean: 6th decade (patients usually older than 40 years)
 - If patients are younger, may be marker of underlying systemic disease
- Sex
 - Male > female (3:2)
- Ethnicity
 - Whites more commonly than other ethnicities

Site

- Helix of ear in men
- Antihelix of ear in women
- Rarely, antitragus may be involved

Presentation

- Painful, solitary nodule on external ear
 - Mean size: 4-7 mm
- Exquisite tenderness, frequently interfering with sleep
- Discrete, oval, gray to red mass with raised or rolled edges
- Central ulcer or depression with horny plug, ± scale crust
- Clinically may simulate carcinoma (basal cell or squamous cell)
- May be marker of diseases with microvascular injury, such as diabetes mellitus or connective tissue disorders

Treatment

- Surgical approaches
 - Needs to be deeply shaved down to underlying cartilage to remove all inflammation
 - Wide excision
 - Hydrodissection (injecting saline) to create cleavage plane followed by narrow skin ellipse

- Greater amount of cartilage can then be removed

Prognosis

- Recurrences (up to 20% of patients) complicate treatment if areas of inflammation are not removed

MICROSCOPIC

Histologic Features

- Epidermal hyperplasia adjacent to keratinaceous (horny) plug
 - Inverted funnel-shaped defect in epidermis
- Transepidermal elimination of necrobiotic material
- Upper dermis displays fibrinoid necrosis or necrobiotic granuloma
- Necrobiotic collagen (collagenolytic destruction) in association with granulation tissue
 - Histiocytes, lymphocytes, and keratinous debris
- Sinus tract created from surface to underlying cartilage
- Eosinophilic degeneration of cartilage
 - Joined by slit-like spaces to central funnel
 - Perichondrium may show fibrosis and inflammation
- Nerve hyperplasia is frequently prominent
 - Suggested reason for exquisite tenderness clinically
- Solar elastosis and telangiectasia concurrently present in upper dermis

DIFFERENTIAL DIAGNOSIS

Relapsing Polychondritis

- Autoimmune disease affecting cartilage with eosinophilic cartilaginous destruction by inflammatory infiltrate
- No epidermal or dermal manifestations

Cystic Chondromalacia (Auricle Pseudocyst)

- Central cystic degeneration of cartilage, followed by granulation tissue and fibrosis
- No epidermal or dermal manifestations

Squamous Cell Carcinoma

- Superficial biopsy makes separation difficult
- Epidermal changes with atypia, mitoses, and invasion

Actinic Keratosis

- Atypia of the keratinocytes with associated solar damage
- Lacks transepidermal elimination, fibrinoid necrosis, collagen lysis or cartilage involvement

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KEY FACTS

TERMINOLOGY

- Benign proliferation of chronic inflammatory cells and granulation tissue in response to longstanding otitis media

CLINICAL ISSUES

- Young (mean: 30 years)
- Male > Female (2:1)
- Patients present with otorrhea, otalgia, bleeding, or sensation of mass, with conductive hearing loss in many
- Affects middle ear, but if tympanic membrane is perforated, external auditory canal mass may be present
- Antibiotics with appropriate sensitivity testing of causative bacteria
- Surgery is 2nd-line therapy for persistent disease after failed antibiotic therapy

IMAGING

- Required to exclude possibility of concurrent cholesteatoma

MACROSCOPIC

- Submit all tissue to exclude **concurrent** cholesteatoma
- Solitary, polypoid, friable, reddish mass

MICROSCOPIC

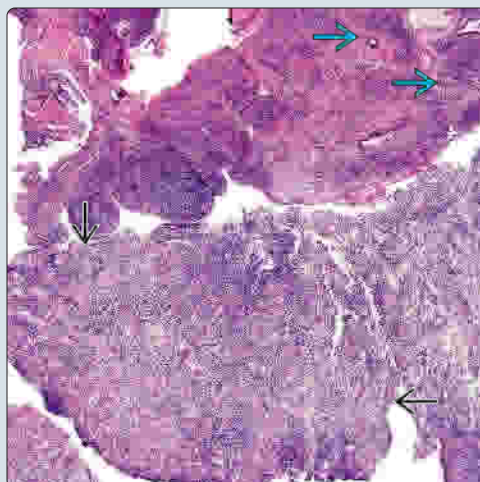
- Polypoid fragments of granulation-type tissue with edematous stroma and high density of capillaries
 - Rich chronic inflammatory infiltrate
- Glandular inclusions within stroma (tunnel clusters) present in longstanding cases

TOP DIFFERENTIAL DIAGNOSES

- Plasmacytoma
- Rhabdomyosarcoma
- Neuroendocrine adenoma of the middle ear

Polypoid Fragments of Tissue

(Left) There are multiple polypoid fragments of tissue in this biopsy sample. Granulation tissue with a rich inflammatory infiltrate is noted [1]. Isolated tunnel clusters are seen [2], a finding seen in longstanding chronic otitis. (Right) If an inflammatory polyp has been present for some time, cholesterol clefts [3] will be seen within the inflammatory background. These appear as empty spaces due to processing artifacts. There is fibrosis and mixed inflammation with blood.

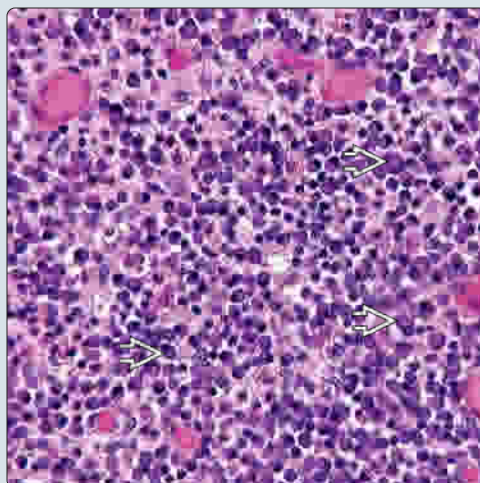


Cholesterol Clefts

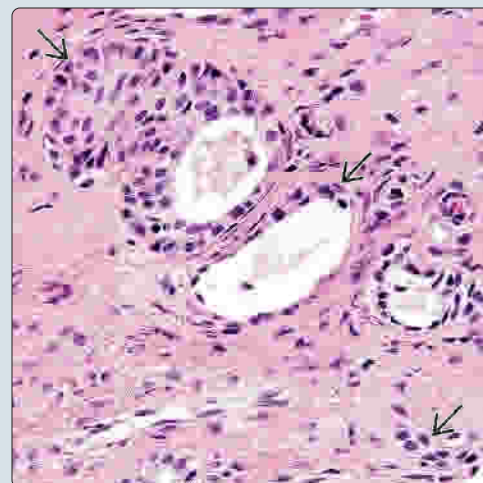


Plasma Cell Infiltrate

(Left) Hematoxylin & eosin shows sheets of plasma cells with a rich vascular tissue. The plasma cells are not atypical, showing eccentric cytoplasm and a "hof" zone [4]. (Right) This H&E shows fibrosis and entrapped surface epithelium [5], referred to as tunnel clusters. This does not represent an invasive tumor.



Tunnel Cluster of Epithelium



TERMINOLOGY**Synonyms**

- Aural polyp

Definitions

- Benign proliferation of chronic inflammatory cells and granulation tissue, usually lined by benign reactive epithelium, in response to longstanding inflammatory process of middle ear

ETIOLOGY/PATHOGENESIS**Infectious Agents**

- Usually a complication of longstanding otitis

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Uncommon
- Age
 - Young (mean: 30 years)
- Sex
 - Male > Female (2:1)

Site

- Middle ear, but if tympanic membrane is perforated, external auditory canal mass may be present

Presentation

- Otorrhea, otalgia, bleeding, or sensation of mass
- Conductive hearing loss
- Rare association with Samter triad

Treatment

- Options, risks, complications
 - Usually complication of longstanding otitis
- Surgical approaches
 - 2nd-line therapy for persistent disease after failed antibiotic therapy
 - Mastoid involvement may require more extensive surgery
 - Performed if cholesteatoma is identified in biopsy/curettage material
- Drugs
 - Antibiotics with appropriate sensitivity testing of causative bacteria

Prognosis

- Excellent

IMAGING**Radiographic Findings**

- Required to exclude possibility of **concurrent** cholesteatoma

MACROSCOPIC**General Features**

- Solitary, polypoid, friable, reddish mass

Sections to Be Submitted

- All tissue submitted to exclude **concurrent** cholesteatoma

Size

- Usually < 2 cm

MICROSCOPIC**Histologic Features**

- Polypoid architecture
- Granulation-type tissue with edematous stroma and high density of capillaries
- Rich chronic inflammatory infiltrate
 - Lymphocytes, plasma cells, histiocytes, and eosinophils
- Plasma cells with Russell bodies and Mott cell formation
- Multinucleated giant cells and calcifications may be seen
- Cholesterol clefts (cholesterol granuloma) may be present
- Glandular inclusions within stroma (tunnel clusters) present in longstanding cases
- **Concurrent** cholesteatoma may be present
 - Stratified squamous epithelium, prominent granular layer, acellular keratinaceous debris

ANCILLARY TESTS**Immunohistochemistry**

- Lymphoid and plasma cell population shows mixture of B and T cells without light chain restriction
- Myoid markers are **negative**

DIFFERENTIAL DIAGNOSIS**Plasmacytoma**

- Monoclonal proliferation of atypical, binucleated plasma cells, showing light chain restriction

Rhabdomyosarcoma

- Small round blue cell neoplasm pattern of embryonal rhabdomyosarcoma may mimic otic polyp
- Strap cells, destructive growth, and muscle immunophenotype

Neuroendocrine Adenoma of the Middle Ear

- a.k.a. middle ear adenoma
- Biphasic glandular proliferation with pseudoinfiltrative pattern
- Nuclei showing neuroendocrine differentiation
- Epithelial and neuroendocrine immunohistochemistry

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KEY FACTS

TERMINOLOGY

- Rare autoimmune disorder against type II collagen, resulting in cartilage destruction

CLINICAL ISSUES

- Very rare
- Mean: 5th-6th decades; female > male (2:1)
- Bilateral auricular involvement is the most common finding (85%)
 - Others sites (order of frequency): Nose, joints, tracheobronchial tree, eye, heart, blood vessels
- **Acute** phase: Ears are red-purple, edematous (swollen), and tender, with noncartilaginous lobule sparing
- **Chronic** phase: Floppy ears, usually after repeated bouts of acute disease
- Associated autoimmune disorder (up to 35%)
- There are antitype II collagen antibodies

- Airway must be secured, while symptoms are managed with corticosteroid, nonsteroidal anti-inflammatory drugs, and immunomodulators


MICROSCOPIC

- Loss of basophilia in cartilaginous plate (earliest change)
- Perichondrium infiltrated by mixed inflammatory infiltrate (neutrophils, lymphocytes, plasma cells, and eosinophils)
- Blurred (instead of sharp) interface between cartilaginous plate and surrounding soft tissues
 - Develops from "outside" in
- Damaged cartilage has moth eaten appearance

TOP DIFFERENTIAL DIAGNOSES

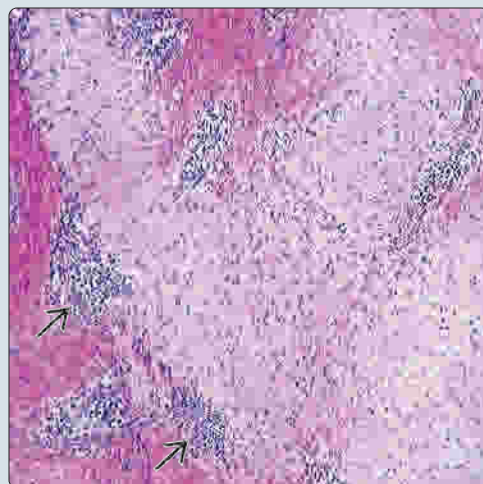
- Necrotizing otitis externa
- Granulomatosis with polyangiitis (Wegener)
- Extranodal NK-/T-cell lymphoma, nasal type
- Cystic chondromalacia

Clinical Photograph of Softened Ear Cartilage


(Left) Clinical photograph shows erythema and distortion of the cartilaginous portion of the pinna and scaphoid regions. Pain is frequently associated with the lesion clinically. (Right) Hematoxylin and eosin shows mixed inflammatory cells destroying the cartilaginous plates, extending from the external surface  in toward the center of the cartilage.

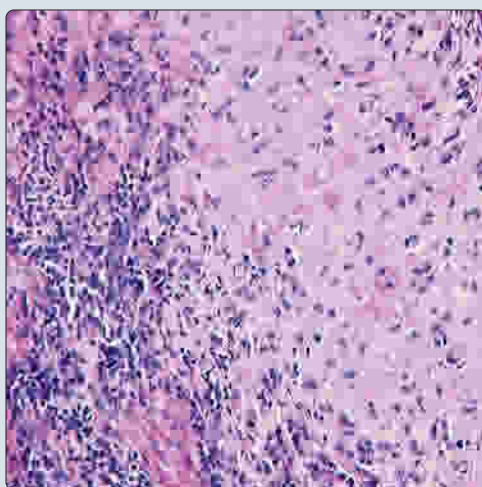


Inflammation on Both Sides of Cartilage Plate

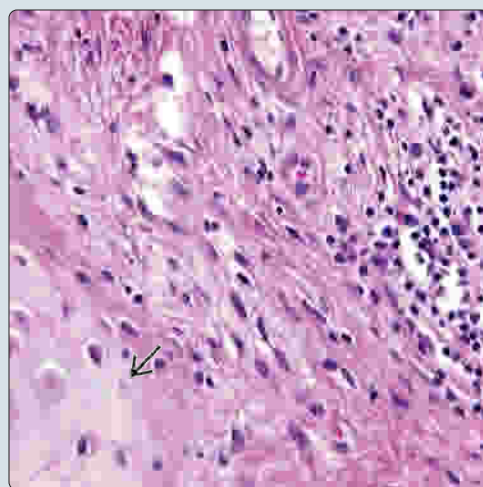


Cartilage Destruction by Inflammatory Cells

(Left) Hematoxylin and eosin shows a loss of cartilaginous structure, demonstrating a slightly bluish appearance with inflammatory cells destroying the periphery, creating an interface chondritis. (Right) Hematoxylin and eosin shows a small collection of inflammatory cells associated with fibrosis adjacent to destroyed cartilage .



Inflammatory Cells Near Cartilage Plate



TERMINOLOGY

Definitions

- Inflammatory, autoimmune disorder against type II collagen, leading to destruction of cartilaginous or proteoglycan-rich tissues

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Autoimmune inflammatory disorder with antibodies against type II collagen
- Susceptibility significantly associated with *HLA-DR4*

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very rare
- Age
 - Mean: 5th-6th decades
- Sex
 - Female > male (2:1)

Site

- Auricle most commonly affected site (85%)
 - Bilateral involvement in nearly all patients
- Others sites (order of frequency): Nose, joints, tracheobronchial tree, eye, heart, blood vessels

Presentation

- **Acute** phase: Ears are red-purple, edematous (swollen), and tender, with noncartilaginous lobule sparing
- **Chronic** phase: Floppy ears, usually after repeated bouts of acute disease
- Other symptoms relate to other anatomic sites
 - Nasal chondritis leads to saddle nose deformity (25-50%)
 - Laryngotracheal disease: Obstruction, laryngeal collapse, and predisposition to pulmonary infections
 - Nonerosive arthritis: 2nd most common clinical site, affecting knees and small joints of hand
 - Cardiovascular disease: Vasculitis (up to 50%)
- Associated autoimmune disorder (up to 35%)
 - Rheumatoid arthritis, Hashimoto thyroiditis, systemic lupus erythematosus, Sjögren syndrome, inflammatory bowel disease, diabetes mellitus, primary biliary cirrhosis, myelodysplastic syndromes, Sweet syndrome

Laboratory Tests

- Antitype II collagen antibodies

Treatment

- Options, risks, complications
 - Airway must be secured
 - Frequently associated with myelodysplasia/leukemia
 - Autologous stem cell transplantation shows promise
- Surgical approaches
 - May be required to maintain patent airway (reconstructive, rib interposition)
- Drugs
 - Variable success dependent on extent of disease
 - May decrease frequency, duration, and severity of flares; fails to halt progression

- Corticosteroid, nonsteroidal anti-inflammatory drugs, and immunomodulators

Prognosis

- Leading cause of death is airway compromise due to tracheobronchial damage
- 10-year survival (55-95%), depending on severity and number of anatomic sites affected
- Negative prognostic factors: Advanced age at diagnosis, anemia, tracheobronchial stricture

MICROSCOPIC

Histologic Features

- Loss of basophilia in cartilaginous plate (earliest change)
- Perichondrium infiltrated by mixed inflammatory infiltrate
 - Neutrophils, lymphocytes, plasma cells, and eosinophils
 - Blurred (instead of sharp) interface between cartilaginous plate and surrounding soft tissues
 - Develops from "outside" in
- Damaged cartilage has moth-eaten appearance
 - Areas are replaced by granulation tissue
 - Eventually, fibrosis replaces granulation tissue

ANCILLARY TESTS

Immunofluorescence

- Granular immunoglobulins and C3 at chondrofibrous junction and within perichondral vessel walls

DIFFERENTIAL DIAGNOSIS

Necrotizing Otitis Externa

- Infection due to *Pseudomonas aeruginosa*, usually rapidly progressive but not cartilage specific

Granulomatosis With Polyangiitis (GPA, Wegener)

- In ear, GPA (Wegener) is not usually consideration
- In sinonasal tract, there is biocollagenolytic, blue, granular necrosis, frequently geographic

Extranodal NK-/T-Cell Lymphoma, Nasal Type

- Highly atypical lymphoid infiltrate with significant necrosis and vascular invasion; no ear involvement typically

Cystic Chondromalacia

- Pseudocyst within center of cartilage, with granulation tissue developing with time
- Tends to develop from "inside" out

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Cystic Chondromalacia (Auricular Pseudocyst)

KEY FACTS

TERMINOLOGY

- Degenerative cystic lesion of ear cartilage
- Pseudocyst or idiopathic cystic chondromalacia

ETIOLOGY/PATHOGENESIS

- Related to acute or repetitive minor trauma (rubbing, earphones, cell phones, helmets)

CLINICAL ISSUES

- Usually young (mean: 35 years)
- Male > > female (9:1)
- Increased incidence in Chinese and Malay men
- Helix or antihelix most common
 - Scaphoid fossa is most common subsite
- Usually painless, fusiform, fluctuant swelling of helix or antihelix with unremarkable skin
- Incision and drainage with curettage is variably successful

MACROSCOPIC

- Central, slit-like cleft filled with < 2 cc of viscous clear to olive oil fluid
- Size: Up to 3 cm

MICROSCOPIC

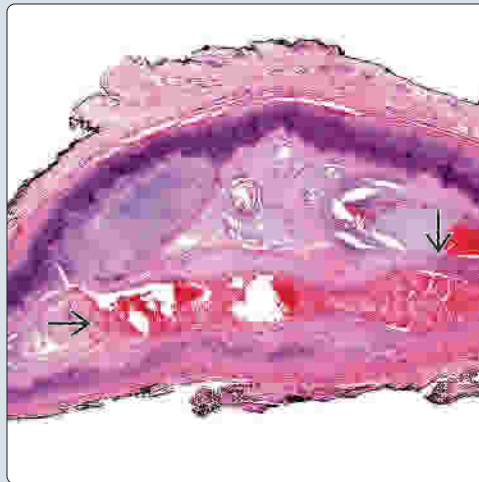
- Central cystic space within cartilage
- No epithelial lining (pseudocyst)
- Irregular inner contour, lined by granulation tissue with plump fibroblasts and inflammatory cells
- Hemosiderin deposits are often present
- Fibrous connective tissue replacement obliterates lumen in longstanding cases

TOP DIFFERENTIAL DIAGNOSES

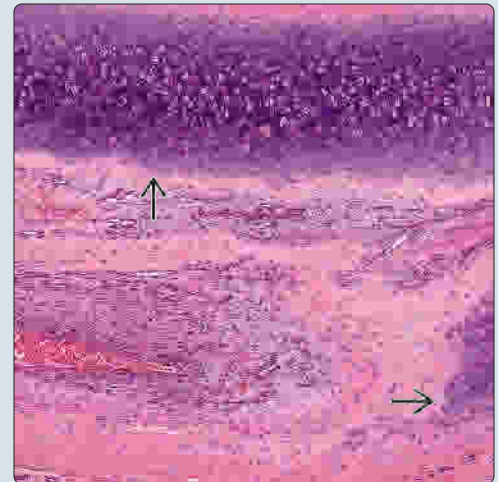
- Relapsing polychondritis
- Chondrodermatitis nodularis helicis
- Traumatic perichondritis

Cartilage Separated by Pseudocyst

(Left) The plates of the ear cartilage are separated by a cystic cavity. The cavity shows no epithelial lining, but there is granulation-type tissue and blood. **(Right)** The central cavity is filled with a granulation tissue and fibrous connective tissue. There is slight degeneration of the cartilage plates, visible at the top and bottom of the field.

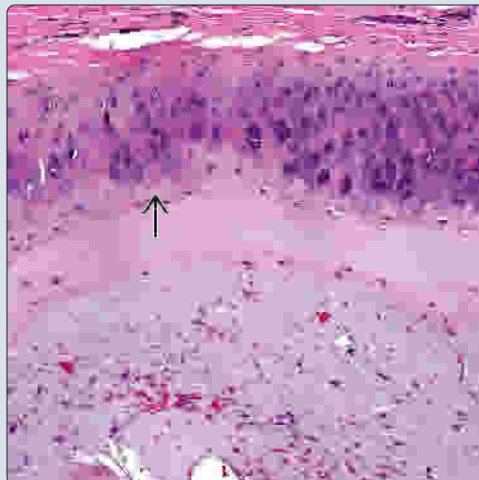


Degeneration and Granulation Tissue

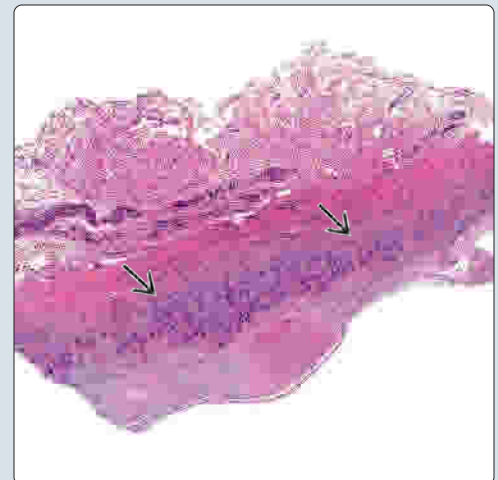


Cystic Fluid and Debris

(Left) There is a layer of cartilage surrounding the area of cyst formation. However, the cyst is filled with fluid and mucinous debris. **(Right)** An unroofing procedure will only yield 1 of the cartilaginous plates. In this setting, the fluid in the cystic cavity will not be seen. Instead, there is a nonepithelial lining with edema and fibrosis.



Unroofed Sample Without Pseudocyst



TERMINOLOGY

Synonyms

- Pseudocyst of auricle (auricular pseudocyst)
- Idiopathic cystic chondromalacia

Definitions

- Degenerative cystic lesion of ear cartilage

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Embryologic fusion defect is possible

Inflammatory

- Cytokine abnormalities

Trauma: Ischemic Necrosis

- Perhaps related to acute or repetitive minor trauma
 - Rubbing, using hard pillows, earphones, cell phones, ear pulling, or helmets
- Abnormal release of lysosomal enzymes
 - Markedly elevated activity of lactate dehydrogenase (LDH), specifically LDH-4 and LDH-5

CLINICAL ISSUES

Epidemiology

- Age
 - Usually young (mean: 35 years)
- Sex
 - Male > > female (9:1)
- Ethnicity
 - Increased incidence in Chinese and Malay men

Site

- Helix or antihelix most common
 - Scaphoid fossa is most common subsite

Presentation

- Unilateral in almost all patients
- Usually painless, fusiform, fluctuant swelling of helix or antihelix with unremarkable skin
- Patients usually seek treatment early in disease development

Laboratory Tests

- LDH isoenzyme patterns of cyst fluid shows LDH 4 and 5 > > LDH 1 and 2

Treatment

- Options, risks, complications
 - Usually treated for cosmetic reasons only
 - Must preserve ear architecture
- Surgical approaches
 - Incision and drainage with curettage is variably successful
 - Unroofing of pseudocyst with insertion of sclerosing agent
 - Tincture of iodine, minocycline, fibrin glue, trichloroacetic acid
 - Needle aspiration followed by suture compression or plaster of Paris cast compression (3 days)

MACROSCOPIC

General Features

- Central, slit-like cleft
- Cyst is filled with viscous clear to olive oil fluid
- Usually < 2 cc of fluid
- If cyst is longstanding, granulation tissue within cavity

Sections to Be Submitted

- Must include cartilage and contents
 - Must know clinical appearance if only unroofing is performed

Size

- Range: Up to 3 cm

MICROSCOPIC

Histologic Features

- Central cystic space within cartilage
- No epithelial lining (pseudocyst)
- Irregular inner contour, lined by granulation tissue with plump fibroblasts and inflammatory cells
- Hemosiderin deposits are often present
- Fibrous connective tissue replacement obliterates lumen in longstanding cases

DIFFERENTIAL DIAGNOSIS

Relapsing Polychondritis

- Painful lesion with rich inflammatory infiltrate that destroys cartilage
- Cartilages all over body affected (autoimmune disorder to type II collagen)

Chondrodermatitis Nodularis Helicis

- Painful lesion with surface ulceration and extrusion of necrobiotic dermal collagen

Traumatic Perichondritis

- Acute infection (*Pseudomonas* or *Proteus*) without cyst formation

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KEY FACTS

TERMINOLOGY

- Acquired abnormal bony growth resulting in fixation of stapes or lateral ossicular chain

ETIOLOGY/PATHOGENESIS

- Otosclerosis shows several genetic linkages
- Only affects bone derived from otic capsule

CLINICAL ISSUES

- ~ 0.5% of population develops clinical otosclerosis
- Mean: Middle age (90% < 50 years)
- Female > male (1.4-2:1) (reflects inheritance pattern differences)
- Foci of abnormal bone deposition include oval and round windows (cochlea)
- Most patients are asymptomatic
- Symptom triad: Progressive conductive hearing loss, normal tympanic membrane, no otitis media
- 3 major categories

- **Classic:** Conductive hearing loss due to stapes fixation
- **Mixed:** Stapes fixation and cochlear involvement
- **Sensorineural:** Cochlear damage without stapes fixation

IMAGING

- High-resolution CT shows characteristic findings and is highly sensitive and specific for diagnosis

MICROSCOPIC

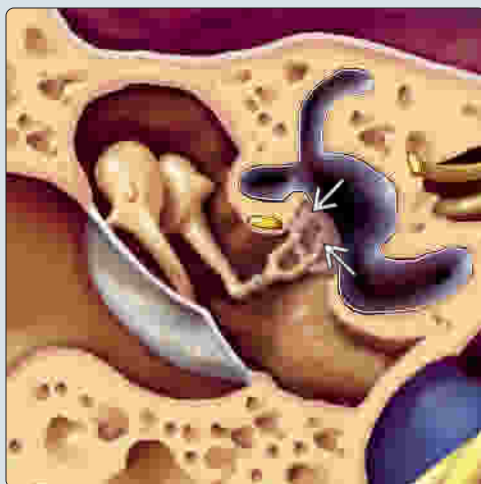
- 3 histologic phases
- **Spongiotic:** Endochondral bone layer resorption by osteoclasts and replaced with highly vascular cellular and fibrous tissue
- **Sclerotic:** Production of immature basophilic bone and filling vascular spaces with collagen fibrils
- **Fibrotic:** Mature acidophilic woven bone

TOP DIFFERENTIAL DIAGNOSES

- Osteogenesis imperfecta, osteopetrosis, Paget disease

Graphic of Otosclerosis Development

(Left) Coronal graphic illustrates findings of fenestral otosclerosis, with a "donut" otospongiotic plaque surrounding the stapes footplate in the oval window. The crisp margins of the oval window are obscured by plaque. The ossicles are normal. (Right) Coronal right temporal bone CT reveals the cochlear disease as well as the fenestral disease. The increased signal is due to the sclerosis. CT is preferable to plain films for this condition.



CT Shows Fenestral Cochlear Otosclerosis

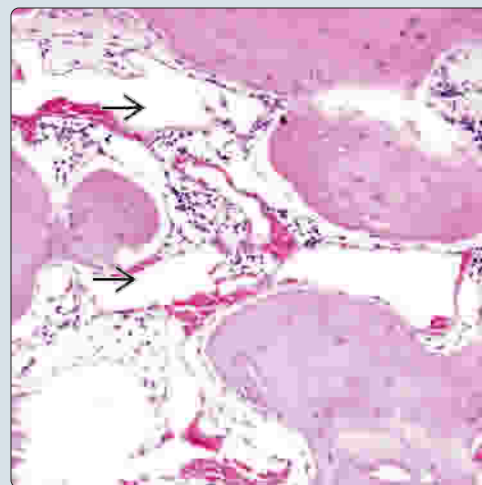


Bone Sclerosis With Fibrous Connective Tissue

(Left) Otosclerosis is recognized histologically by increased density and thickness of bone distorting the affected areas. The resultant bone can appear similar to cortical bone. (Right) Vascular channels can be prominent, associated with bone deposition (mature acidophilic woven bone).



Vascular Channels in Otosclerosis



TERMINOLOGY

Definitions

- Acquired abnormal bony growth resulting in fixation of stapes or lateral ossicular chain

ETIOLOGY/PATHOGENESIS

Inherited

- Otosclerosis shows several genetic linkages, with variable penetrance and expression

Pathophysiology

- Otosclerosis only affects bone derived from otic capsule
- Otosclerosis is characterized by increased rate of bone remodeling in otic capsule
- Disturbed balance between cell survival and apoptosis
- Disease development in 4 stages

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~ 0.5% of population develops clinical otosclerosis
- Age
 - Mean: Middle age (90% < 50 years)
 - Younger in inherited cases
- Sex
 - Female > male (1.4-2:1) (different inheritance patterns)
- Ethnicity
 - Whites > > Asians, blacks, South American Indians

Site

- Foci of abnormal bone deposition include oval and round windows (cochlea)
 - Fixation of stapes footplate to cochlea oval window

Presentation

- Most patients are asymptomatic
- Symptom triad: Progressive conductive hearing loss, normal tympanic membrane, no otitis media
 - Faint pink tinge to cochlear promontory: Schwartze sign
- If symptomatic, hearing loss is most common symptom
 - Conductive hearing loss most common (low frequencies) (Rinne &/or Weber tests)
 - Sensorineural loss (high frequency) less frequent (10%) and late manifestation
 - Hearing loss in 0.2-0.5% of population due to ankylosis of footplate
- Often unilateral initially but nearly always bilateral
- 3 major categories
 - Classic:** Conductive hearing loss due to stapes fixation
 - Mixed:** Stapes fixation and cochlear involvement resulting in mixed hearing loss
 - Sensorineural:** Cochlear damage without stapes fixation
- Vestibular findings (imbalance, vertigo) in ~ 10%

Treatment

- Medical management or surgery can be used
- Stapedectomy or stapedotomy (microdrill or laser) can restore conductive hearing loss
 - Cochlear implantation of prosthesis

- Medical
 - Hearing aids: Early in disease management
 - Fluoride additive: Slows disease progression

IMAGING

General Features

- High-resolution cone beam CT shows characteristic findings and is highly sensitive and specific for diagnosis
 - Separated into 2 types: Fenestral or cochlear otosclerosis

MICROSCOPIC

Histologic Features

- Fibrosis/sclerosis within middle ear bones
- 3 histologic phases
 - Spongiotic:** Endochondral bone layer resorption by osteoclasts and replaced with highly vascular cellular and fibrous tissue
 - Bone resorption around existing vessels, resulting in dilated vascular spaces
 - Sclerotic:** Production of immature basophilic bone and filling vascular spaces with collagen fibrils
 - Blue mantles of Manasse
 - Fibrotic:** Mature acidophilic woven bone
- May see atypical shapes and arrangements of osteons, resulting in larger differentiated osteons with irregularities in structure
- Otospongiosis (severe dilatation of many Volkmann canals)

ANCILLARY TESTS

Immunohistochemistry

- Active otosclerosis shows differentially increased expression of bone morphogenetic protein (BMP) 2, 4, 5, and 7 compared to non-otosclerotic bone

DIFFERENTIAL DIAGNOSIS

Osteogenesis Imperfecta

- All layers of otic capsule affected, with greater degree of structural disorganization and larger resorption spaces

Osteopetrosis

- Increased density of bone throughout entire body

Paget Disease

- Excessive bone resorption and formation due to activated osteoclasts
- Moth-eaten appearance eroding peripheral otic capsule

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KEY FACTS

TERMINOLOGY

- Definition: Inflammatory process initiated by soft tissue deposition of monosodium urate (MSU) crystals

ETIOLOGY/PATHOGENESIS

- Hyperuricemia is main factor facilitating MSU crystal formation
- Urate crystals provoke inflammatory response from leukocytes, resulting in phagocytosis

CLINICAL ISSUES

- Gout is most prevalent inflammatory arthritis in developed countries
- Older male patients (male > female [3:1])
- Progression: Asymptomatic hyperuricemia, acute attacks, tophaceous deposits
- Ear is most common site of tophus formation in head and neck
 - Tophus is irregular, painful skin deposit

- Acute attacks managed with rest, immediate treatment with colchicine, and antiinflammatory agents

MACROSCOPIC

- Tophi have white, chalky consistency when cut and range from 1-6 cm

MICROSCOPIC

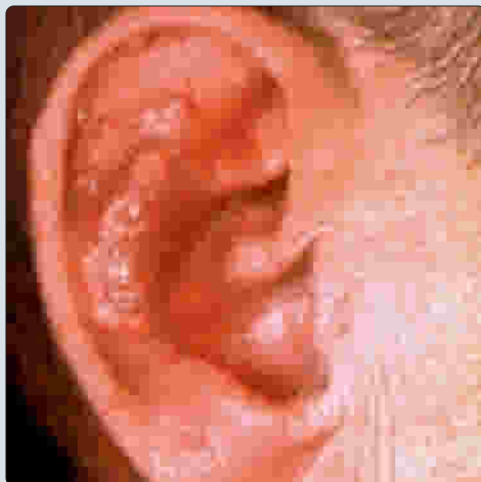
- Tophi: Urate crystals surrounded by chronic mononuclear and giant cell reactions in soft tissues
- Skin overlying tophus frequently ulcerates
- Fluid should be examined rapidly at room temperature
- Under direct polarized light crystals are strongly birefringent
 - Yellow: Aligned parallel to light
 - Blue: Aligned perpendicular to light

TOP DIFFERENTIAL DIAGNOSES

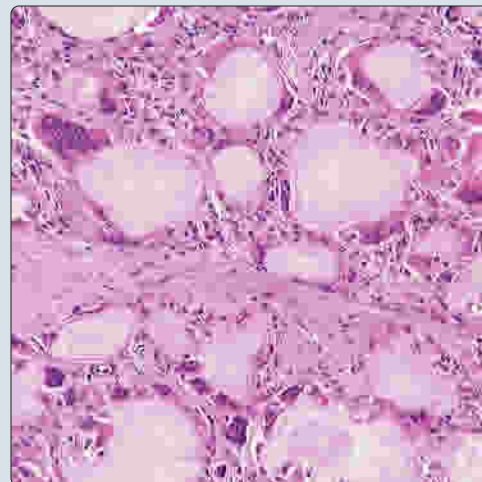
- Rheumatoid nodules
- Foreign body giant cell reaction

Tophus on Pinna

(Left) Tophaceous gout presents as irregularly shaped deposits under the skin and often present on the ear. They are very painful to compression. Cut surfaces will have a white, chalky appearance. (Right) The foreign body giant cell reaction is remarkable, with crystal outlines easily identified in each collection. This is a characteristic appearance for a gouty tophus.



Foreign Body Giant Cell Reaction

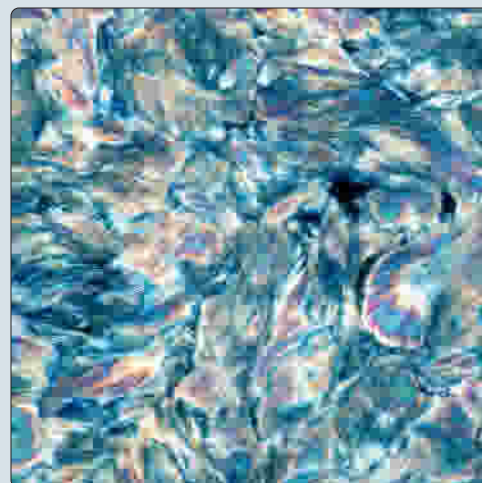


Amorphous Urate Crystals

(Left) Gouty deposits show amorphous collections of crystals surrounded by foreign body giant cells and scattered inflammatory cells. (Right) Methylene blue preserved crystals examined under direct polarized light show needle-shaped crystals that appear very bright against the dark background. Examination should be done quickly to avoid degradation. Yellow (aligned parallel) and blue (aligned perpendicular) colors are related to crystal direction to the light.



Gout Crystals Under Polarized Light



TERMINOLOGY**Definitions**

- Inflammatory process initiated by soft tissue deposition of monosodium urate (MSU) crystals

ETIOLOGY/PATHOGENESIS**Pathogenesis**

- Purine metabolism results in end product of uric acid by conversion of xanthine by xanthine oxidase
- Hyperuricemia is main factor facilitating MSU crystal formation
 - Urate is filtered by kidney, with > 90% resorbed
 - Main reason for increased urate is impaired renal function
 - Urate controlled by purine ingestion, liver production, recycling, degradation
 - Overproduction associated with excessive alcohol intake, fructose consumption
- Urate crystals provoke inflammatory response from leukocytes and synovial cells
 - Phagocytosed by monocytes as particles

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Gout is most prevalent inflammatory arthritis in developed countries
 - Increasing, especially in older population
 - Increased in patient with high meat, seafood, and fructose consumption; high alcohol intake
- Age
 - Older patients
- Sex
 - Male > Female (3:1)
 - Females increased in postmenopausal years (decreased estrogen is uricosuric)
- Ethnicity
 - Lower incidence in blacks, Japanese, Native Americans

Site

- Ear is most common site of tophus formation in head and neck, followed by larynx and thyroid cartilages

Presentation

- Initial symptoms of gout are usually monoarticular arthritis and pain, usually of 1st toe
- **Ear:** Irregular, painful deposits in skin
- Drugs can also precipitate acute gout through altered uric acid concentrations
- Solid organ transplant patients develop hyperuricemia, with ~ 10% developing gout

Laboratory Tests

- Normal plasma urate levels: 200-410 $\mu\text{mol/L}$ (3.3-6.9 mg/dL), with gout patients showing elevation

Treatment

- Options, risks, complications
 - Acute attacks managed with rest, immediate treatment with colchicine, and antiinflammatory agents

- Aim to maintain urate concentration below saturation point for MSU

• **Drugs**

- Wide armamentarium of drugs to treat hyperuricemia and effects

Prognosis

- Disease waxes and wanes
- Polyarticular arthritis, renal injury, and nephrolithiasis are complications

MACROSCOPIC**General Features**

- Most specimens submitted as fluids for crystal examination
- Tophi will show white, chalky consistency when cut

Size

- Tophi range: 1-6 cm

MICROSCOPIC**Histologic Features**

- Tophi: Urate crystals surrounded by chronic mononuclear and giant cell reactions in soft tissues
- Skin overlying tophus ulcerates
 - MSU crystals are dissolved by formalin-based preservatives
 - Leave basophilic granular deposits on light microscopy when dissolved
 - Specimens are better preserved when submitted in ethanol
- Fluid should be examined rapidly at room temperature
 - Formation and solubility of crystals are affected by temperature and pH
 - Under direct polarized light crystals are strongly birefringent
 - Yellow when aligned parallel to light
 - Blue when aligned perpendicular to light
 - Bright against black background

DIFFERENTIAL DIAGNOSIS**Rheumatoid Nodules**

- Necrotizing granulomatous inflammation with peripherally palisaded epithelioid histiocytes
- Vasculitis may be present

Foreign Body Giant Cell Reaction

- Variety of substances may be phagocytosed, but they can be easily separated from urate crystals

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KEY FACTS

TERMINOLOGY

- Benign hyperostotic outgrowths of bony external auditory canal (EAC)
- Surfer's ear
- Cold water ear

ETIOLOGY/PATHOGENESIS

- West coast surfers have more severe exostoses in right vs. left ear

CLINICAL ISSUES

- Incidence is related to patients with chronic history of prolonged cold water exposure
 - Swimmers, cold water surfers, scuba divers, whitewater kayaking
 - Prevalence in **surfers**: 70-80%
- Male > > female
- Almost always bilateral
- Conductive hearing loss

- Typically benign lesion, requiring no treatment
- Otoscopic view shows circumferential submucosal narrowing
- Ear plugs may decrease progression

IMAGING

- Benign, broad-based, bilateral, circumferential overgrowth of osseous EAC with normal overlying soft tissues

MICROSCOPIC

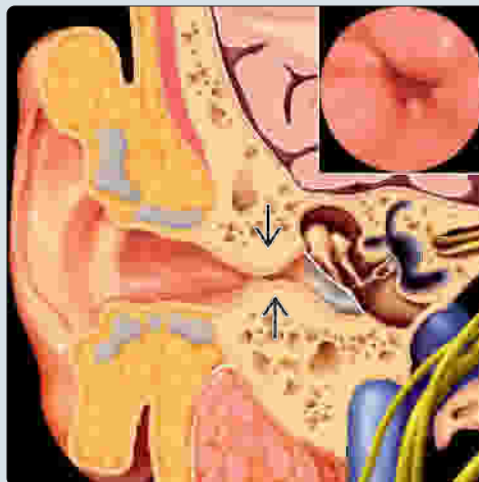
- Histologically composed of broad-based lamellar bone with overlying cartilage cap
- Similar to normal epiphyseal growth
- Cartilage cap may be very thinned or have matured fully to bone
- In many cases, exostoses and osteomata cannot be reliably separated without radiographic/clinical information

TOP DIFFERENTIAL DIAGNOSES

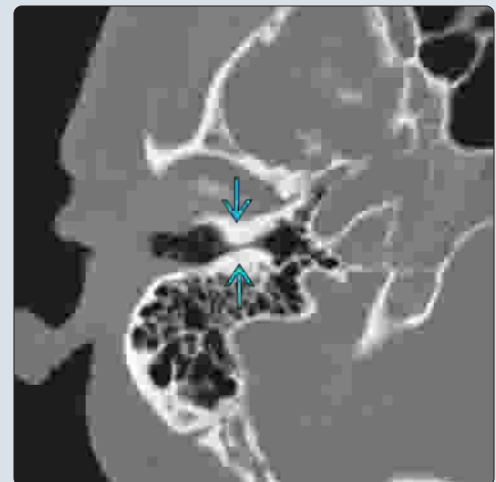
- Osteoma

Graphic of Exostosis With Otoscopic View

(Left) Coronal graphic shows benign-appearing bony overgrowth of the right external auditory canal (EAC) in a case of EAC exostoses. Insert shows otoscopic view of circumferential submucosal EAC narrowing. (Right) T-bone CT of the right ear shows broad-based osseous EAC encroachment on both anterior and posterior walls in this case of EAC exostoses. Note the EAC lumen is severely narrowed.



CT of Broad-Based Osseous Narrowing

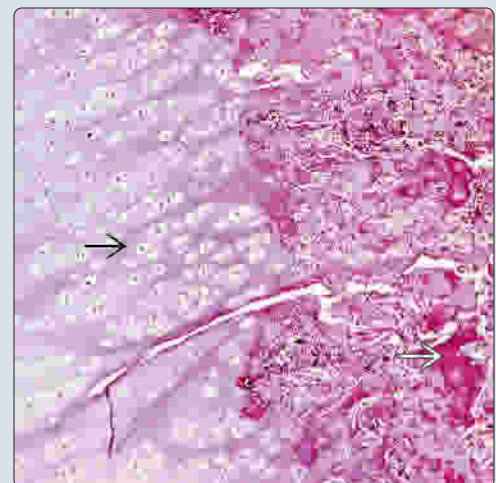


Bone Below an Intact Squamous Epithelium

(Left) There is an intact squamous epithelium of the EAC overlying the bone that comprises this exostosis. This case did not show cartilage. (Right) At low-power, sections will show prominent cartilage and underlying bone. This is an example of endochondral ossification, frequently seen in this lesion.



Endochondral Ossification



TERMINOLOGY**Abbreviations**

- External auditory canal (EAC)

Synonyms

- Surfer's ear
- Cold water ear

Definitions

- Benign hyperostotic outgrowths of bony EAC

ETIOLOGY/PATHOGENESIS**Environmental Exposure**

- Cold water exposure causes more severe external auditory exostosis, possibly by 2 methods
 - Irritation of EAC
 - Increased vascular flow
- Other environmental factors may play role
 - Climatologic factors
 - West coast surfers have more severe exostoses in right vs. left ear
 - Probably due to northerly wind in coldest months as surfers face west
 - Evaporative cooling is greater in wind-exposed ear

CLINICAL ISSUES**Epidemiology**

- Incidence
 - While uncommon, incidence is related to patients with prolonged cold water exposure
 - Prevalence in **surfers**: 70-80%
 - Incidence in **salt water** swimmers: 6%
 - Incidence in **fresh water** swimmers: 5%
- Age
 - Usually young patients
- Sex
 - Male > > female
- Ethnicity
 - Very low to absent in blacks (reason unknown)

Site

- Almost always bilateral
- Lesion usually present medial to isthmus of EAC
 - Both anterior and posterior for vast majority
 - Begins at medial osseous EAC

Presentation

- Conductive hearing loss
 - Although bilateral disorder, 80% of patients present with unilateral symptoms
- Chronic history of prolonged cold water exposures
 - Swimmers, cold water surfers, divers (scuba), whitewater kayakers
- Otitis externa, tinnitus, otalgia

Endoscopic Findings

- Otoscopic view shows circumferential submucosal narrowing

Treatment

- Options, risks, complications
 - Typically benign lesion, requiring no treatment
 - Ear plugs may decrease progression
 - If surgery is used, postsurgical complications can be seen in 5% and include
 - Canal stenosis, temporal-mandibular joint prolapse, sensorineural hearing loss, persistent tympanic membrane perforation
- Surgical approaches
 - EAC drilling is surgical management of choice, if patients are symptomatic
 - Potential surgical problems include
 - Skin over exostosis is frequently traumatized by drill
 - Tympanic membrane may be perforated, potentially damaging ossicular chain &/or chorda tympani nerve
 - Temporomandibular joint dehiscence

IMAGING**General Features**

- Benign, broad-based, bilateral, circumferential overgrowth of osseous EAC with normal overlying soft tissues
- Noncontrast CT with bone algorithm of temporal bone

MACROSCOPIC**General Features**

- Identified near tympanic annulus, at tympanomastoid and tympanosquamous sutures

MICROSCOPIC**Histologic Features**

- Broad-based bone with overlying cartilage cap
 - Similar to normal epiphyseal growth
 - Cartilage cap may be very thinned or have matured fully to bone
- Histologically composed of broad-based lamellar bone
 - In many cases, exostoses and osteomata cannot be reliably separated without radiographic/clinical information

DIFFERENTIAL DIAGNOSIS**Osteoma**

- Location (lateral to isthmus) and clinical symptoms different from exostoses

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KEY FACTS

TERMINOLOGY

- Scar with prominent thickened and eosinophilic bundles of collagen extending beyond original wound
 - Keloid shows proliferative growth beyond margins of scar and remains persistent
 - Hypertrophic scar is contained to original wound and may regress over time

CLINICAL ISSUES

- Most common in patients < 30 years
- More common in black patients
- Earlobe is most common site within head and neck
 - Typically follows ear piercing or other trauma
- Mass is most common
- Classified into 5 different types for management purposes
 - Sessile, single nodular pattern; pedunculated; sessile, multinodular pattern; buried; and mixed type

- Many treatment modalities, including intralesional corticosteroids, topical applications, cryotherapy, surgical excision, radiation therapy, silicone gel sheeting, pressure therapy, and laser therapy

MACROSCOPIC

- Large, nodular, dermal-based lesion, with firm, white cut surface

MICROSCOPIC

- Dense proliferation of thickened, hyalinized collagen bundles in dermis
- Decreased vessels compared to conventional and hypertrophic scars
- Overlying epidermis may show atrophy

TOP DIFFERENTIAL DIAGNOSES

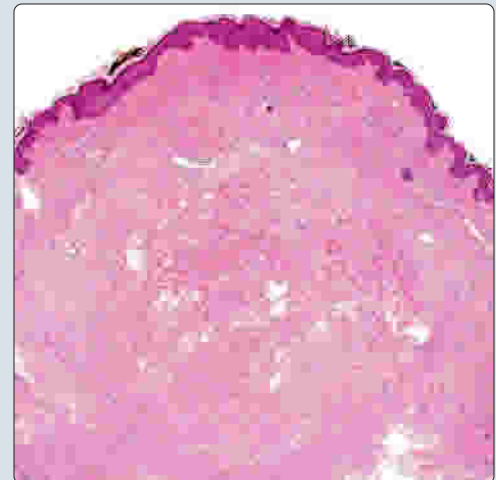
- Hypertrophic scar
- Desmoplastic melanoma
- Nodular fasciitis

Clinical Photo of Large Earlobe Keloid

(Left) This black patient shows a very large and disfiguring ear lobe keloid. Areas of scar and skin atrophy can be seen on the surface. Previous trauma (ear piercing) is a common reported finding. **(Right)** Low-power magnification shows a polypoid skin lesion with dense dermal collagen, showing a more eosinophilic appearance than the surrounding fibrosis.

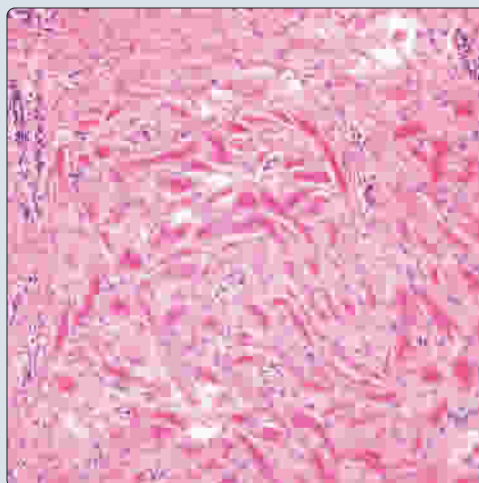


Heavy Keloidal Collagen Deposition

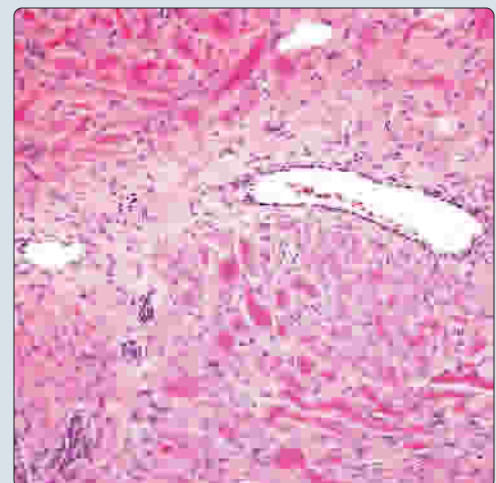


Dense, Acellular Collagen Deposition

(Left) High-power magnification shows a proliferation of thickened, hyalinized eosinophilic collagen bundles with increased numbers of stromal fibroblasts and scattered lymphocytes. This is a characteristic histologic finding for keloid. **(Right)** Superficial portion of a keloid shows telangiectatic vessels surrounded by thickened collagen bundles. The bundles of collagen are haphazard and dense.



Telangiectatic Vessels in Keloid



TERMINOLOGY**Synonyms**

- Scar with keloidal collagen deposition

Definitions

- Scar with prominent thickened and eosinophilic bundles of collagen extending beyond original wound
 - Keloid shows proliferative growth beyond margins of scar and remain persistent
 - Hypertrophic scar is contained to original wound and may regress over time

ETIOLOGY/PATHOGENESIS**Idiopathic**

- Fibroblasts from keloids show decreased apoptosis
- Many cytokines implicated in stimulating fibroblasts, including TGF- β and IL-15
- Genetic influence is likely

CLINICAL ISSUES**Epidemiology**

- Age
 - Most common in patients < 30 years
- Ethnicity
 - More common in black patients
 - Least common in white patients

Site

- Earlobe is most common site
 - Typically follows ear piercing or other trauma
 - Usually develops within a few months

Presentation

- Mass is most common
- Scar growing beyond confines of original wound
- Often erythematous, pruritic lesions with predilection for earlobe in black patients
- Classified into 5 different types for management purposes:
 - Sessile, single nodular pattern; pedunculated; sessile, multinodular pattern; buried; and mixed type

Treatment

- Options, risks, complications
 - Potentially disfiguring with high recurrence risk
 - Many treatment modalities, including intralesional corticosteroids, topical applications, cryotherapy, surgical excision, radiation therapy, silicone gel sheeting, pressure therapy, and laser therapy
 - Treatment approach depends on distribution, size, thickness, and consistency of lesion
- Surgical approaches
 - Complete excision, accompanied by concurrent steroid injections or radiotherapy to decrease risk of recurrence
- Drugs
 - Direct injection of steroids is often first-line treatment

Prognosis

- Persistence and recurrence are common
- No increased risk of malignancy

MACROSCOPIC**General Features**

- Large, nodular, dermal-based lesion
- Firm, white cut surface

MICROSCOPIC**Histologic Features**

- Dense proliferation of thickened, hyalinized collagen bundles in dermis
- May be background of conventional or hypertrophic scar
 - Contains smaller collagen bundles and perpendicular vessels
- Decreased vessels compared to conventional and hypertrophic scars
 - Superficial telangiectatic vessels often present
 - Associated with mild chronic inflammation
- Overlying epidermis may show atrophy
- Increased fibroblasts, lymphocytes, and mast cells are usually present

DIFFERENTIAL DIAGNOSIS**Hypertrophic Scar**

- Not as clinically elevated as keloid, and usually confined to extent of injury/surgery
- Lacks characteristic hyalinized collagen bundles of keloid
- More small, perpendicularly oriented vessels
- Lacks telangiectasia
- Overlapping cases may be seen; may be diagnosed as "hypertrophic scar with focal keloidal collagen"

Desmoplastic Melanoma

- Unlikely, but rarely may enter differential diagnosis if no history of trauma or previous treatment (biopsy or excision)
- Reexcision specimens of desmoplastic melanoma may show keloidal collagen
- S100 protein and SOX10 immunohistochemical stains should be **positive**
 - Increased numbers of dermal dendritic cells may be seen in scars
 - Keloid should not show spindled morphology of desmoplastic melanoma cells

Nodular Fasciitis

- May show focal keloidal collagen
- Background shows classic features of nodular fasciitis with loose, tissue culture appearance, extravasated erythrocytes and giant cells

DIAGNOSTIC CHECKLIST**Pathologic Interpretation Pearls**

- Nodular, elevated lesion compared to adjacent skin
- Thickened, hyalinized eosinophilic collagen bundles
- Often see background of hypertrophic scar

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1. Nicoletti G et al: Clinical and histologic effects from CO2 laser treatment of keloids. *Lasers Med Sci*. 28(3):957-64, 2013
2. Thompson LD: Skin keloid. *Ear Nose Throat J*. 83(8):519, 2004

KEY FACTS

TERMINOLOGY

- Angiolymphoid hyperplasia with eosinophilia (ALHE) or epithelioid hemangioma
- Benign vascular tumor with well-formed, immature blood vessels, most of which are lined by plump, epithelioid (histiocytoid) endothelial cells with prominent inflammatory component, rich in eosinophils

CLINICAL ISSUES

- Wide range; mean: 3rd to 5th decades
- Female > male
- Head (scalp, ears) most commonly affected
- Nodule or mass in subcutaneous tissues (**not** lymph nodes), present for up to 12 months
- Pink to red-brown (hyperpigmented), dome-shaped papules or nodules
- Excision, but recurrences, regrowth, or persistence after surgery requires follow-up

MICROSCOPIC

- Multiple lobules of inflammatory elements with increased vascularity on low power
- Proliferation of small immature capillary type to medium vessels usually without lumina
- Endothelial cells are enlarged with epithelioid or histiocytic appearance
 - Endothelial cells may have cytoplasmic vacuolization
 - May have solid appearance
- Many eosinophils, lymphocytes, and mast cells, although eosinophil number can vary greatly

TOP DIFFERENTIAL DIAGNOSES

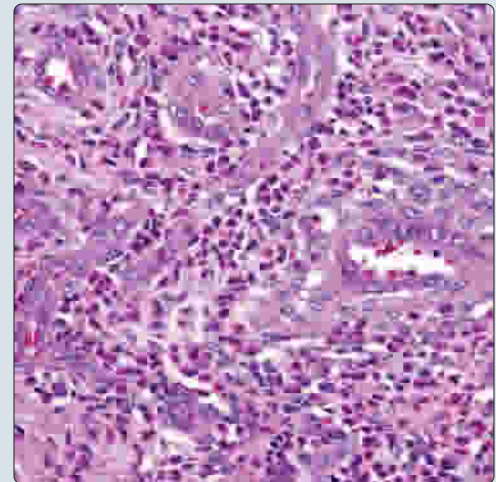
- Papillary endothelial hyperplasia, Kimura disease
- Angiosarcoma, metastatic papillary thyroid carcinoma

Subepithelial Vascular Proliferation

(Left) Hematoxylin and eosin shows an intact surface epithelium with a richly vascularized stroma containing lymphoid elements. Eosinophils are present, imparting a bright red appearance at this low magnification. (Right) There are sheets of eosinophils in the background stroma. The vascular spaces are lined by endothelial cells that are enlarged and prominent. There is no atypia and no anastomosing.

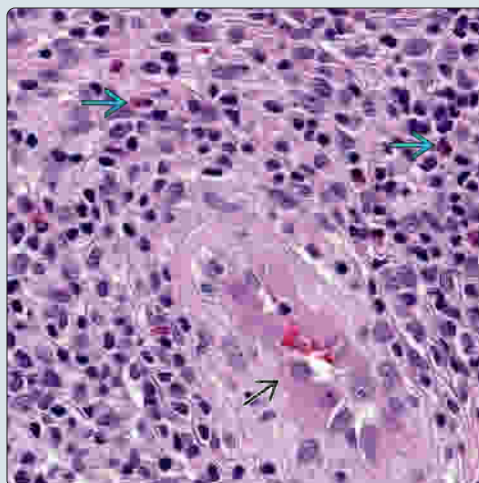


Vascular Proliferation With Eosinophils

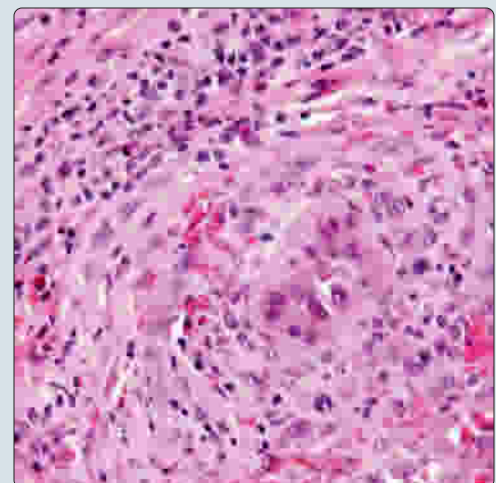


High Endothelial Cells

(Left) The endothelial cells are enlarged and partly occlude the lumen. Eosinophils are noted in the background. Sometimes the eosinophils are inconspicuous. (Right) Hematoxylin and eosin shows endothelial hyperplasia with a thickened vessel wall and increased inflammatory cells, including eosinophils, in the surrounding tissue. Note the extravasated erythrocytes.



Endothelial Hyperplasia



TERMINOLOGY

Abbreviations

- Angiolymphoid hyperplasia with eosinophilia (ALHE)

Synonyms

- Epithelioid hemangioma

Definitions

- Benign vascular tumor with well-formed, immature blood vessels, most of which are lined by plump, epithelioid (histiocytoid) endothelial cells with a prominent inflammatory component, especially eosinophils

ETIOLOGY/PATHOGENESIS

Reactive

- History of trauma; larger vessels show damage with prominent inflammatory component

Neoplastic

- May represent benign neoplasm, with evidence of clonal T-cell population in some cases

CLINICAL ISSUES

Epidemiology

- Age
 - Wide range; mean: 3rd to 5th decades
- Sex
 - Female > male
- Ethnicity
 - **Not** increased in Asian patients (i.e., **not** Kimura disease)

Site

- Head (scalp, ears) most commonly affected
 - Digits next most common

Presentation

- Nodule or mass in subcutaneous tissues (**not** lymph nodes), present for up to 12 months
- Pain &/or pruritus; easily excoriate or bleed
- Pink to red-brown (hyperpigmented), dome-shaped papules or nodules
- Nodules may be multiple, ultimately coalescing
- Rarely may spontaneously regress/involute

Laboratory Tests

- Peripheral blood eosinophilia in some patients
- **No** elevated IgE levels

Treatment

- Excision, but recurrences, regrowth, or persistence after surgery requires follow-up

Prognosis

- Excellent, although with frequent recurrence

MACROSCOPIC

General Features

- May resemble lymph node due to circumscription and peripheral inflammation

Size

- Mean: 0.5-2 cm; rarely > 5 cm

MICROSCOPIC

Histologic Features

- Multiple lobules of inflammatory elements with increased vascularity on low power
- Surface usually intact, but can be excoriated
- Proliferation of small immature capillary type to medium vessels usually without lumina
- May be attached to or associated with larger vessels
- May have solid appearance
- Endothelial cells are enlarged with epithelioid or histiocytic appearance
- Endothelial cells may have cytoplasmic vacuolization
- Endothelial nuclei are enlarged
- Many eosinophils, lymphocytes, and mast cells, although eosinophil number can vary greatly
- Lymphoid follicles sparse and poorly formed

ANCILLARY TESTS

Immunohistochemistry

- Endothelial cells **positive** for CD31, CD34, FLI-1, FVIIIIRAg
- Actin (+) vascular muscle walls
- IgE(+) mast cells, but no IgE on follicular dendritic cells
 - Mast cells have IgE receptors but distinct from follicular dendritic cells

DIFFERENTIAL DIAGNOSIS

Papillary Endothelial Hyperplasia

- Reactive process limited to intravascular space(s)
- Papillary projections of enlarged endothelial cells

Kimura Disease

- Asian men with large disfiguring preauricular lymph node masses; peripheral eosinophilia
- Reactive lymphoid follicles with follicular lysis, eosinophilic abscesses, polykaryocytes, and IgE deposition

Angiosarcoma

- Highly atypical, mitotically active, freely anastomosing endothelial proliferation
- Usually shows necrosis and hemorrhage

Metastatic Papillary Thyroid Carcinoma

- Epithelioid cells with intranuclear cytoplasmic inclusions in lymphoid stroma
- **Positive:** TTF-1, thyroglobulin, pax-8

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KEY FACTS

TERMINOLOGY

- Rare granulomatous disease often associated with abnormal reaction to infectious organisms

ETIOLOGY/PATHOGENESIS

- End stage of inability of macrophages to destroy phagocytized bacteria
- Organ transplantation, malignancy, diabetes mellitus, AIDS, tuberculosis, malnutrition, sarcoidosis, allergies

CLINICAL ISSUES

- Rare; ear most commonly affected head & neck site
- Male > female
- Usually adults, but can be any age

MACROSCOPIC

- Yellow-brown soft plaques characterized by central navel or ulcer, hyperemic at edge

MICROSCOPIC

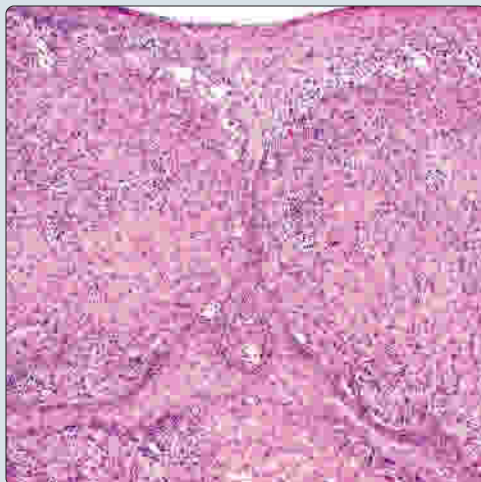
- Marked pseudoepitheliomatous hyperplasia
- Subepithelial spaces filled with sheets of eosinophilic histiocytes, most of which contain granular cytoplasmic material
- Large, granular, or foamy histiocytes with low nuclear:cytoplasm ratio (no atypia)
- Michaelis-Gutmann bodies are well-formed blue, calcific bodies, both intracytoplasmic and stromal
 - Targetoid and concentrically laminated
 - Black stain with von Kossa (calcium stain)
 - Blue stain with Prussian blue (iron stain)

TOP DIFFERENTIAL DIAGNOSES

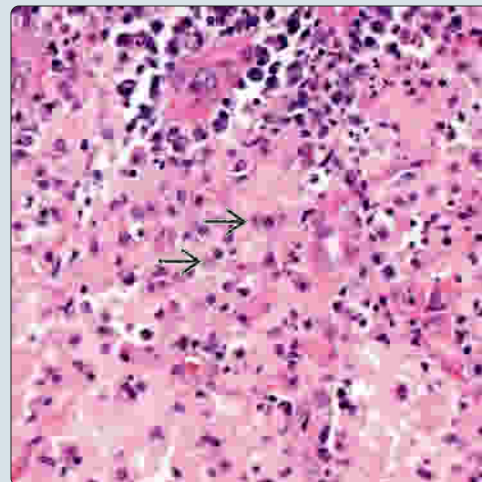
- Granular cell tumor, pseudoepitheliomatous hyperplasia, Langerhans cell histiocytosis, lymphoma, poorly differentiated carcinoma, alveolar soft part sarcoma

PEH With Histiocytes and Inflammation

(Left) Hematoxylin and eosin of pseudoepitheliomatous hyperplasia (PEH) shows squamous epithelium overlying a mixed inflammatory infiltrate with sheets of histiocytes. (Right) Hematoxylin and eosin shows sheets of histiocytes with mixed inflammatory infiltrate and targetoid bodies [2].

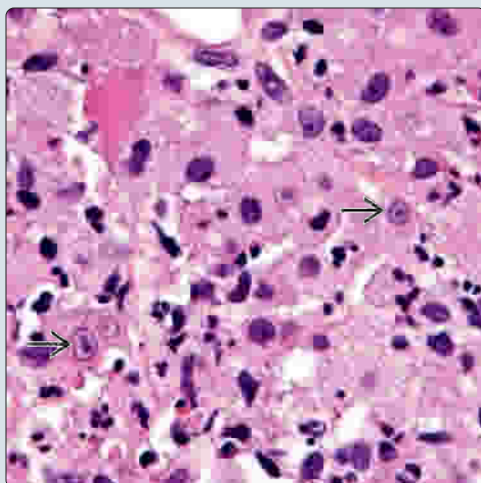


Targetoid Bodies With Histiocytes

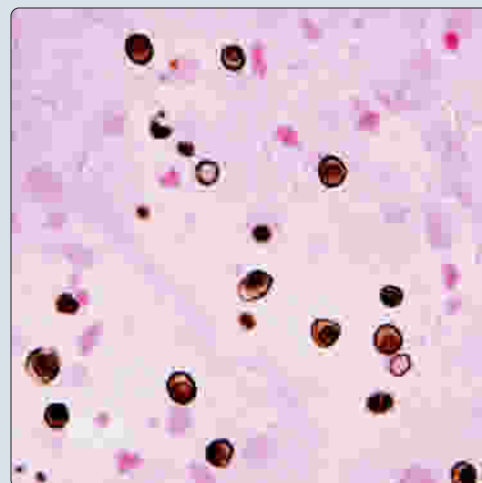


Michaelis-Gutmann Bodies

(Left) Foamy histiocytes have eosinophilic cytoplasm and the characteristic intracytoplasmic calcific inclusions (Michaelis-Gutmann bodies [2]) diagnostic for this entity. (Right) von Kossa (calcium stain) highlights the Michaelis-Gutmann bodies by yielding a black stain. This is distinctive, as there is a targetoid appearance, different from usual calcium staining in other disorders.



Calcium Stain Highlights Michaelis-Gutmann Bodies



KEY FACTS

TERMINOLOGY

- Reactive process of unknown pathogenesis characterized by
 - Formation of multiple cartilaginous nodules in synovium many becoming detached and float within joint space

ETIOLOGY/PATHOGENESIS

- Condition in which foci of cartilage develop in synovial membrane of joint
 - Apparently occurring through metaplasia of sublining connective tissue of synovial membrane

CLINICAL ISSUES

- Mean age: 45-47 years; female > male (2.5:1)
- Symptoms include pain and swelling
- Treatment: Complete removal of all tissue
- Symptoms are nonspecific, mimicking other disorders
 - May present with preauricular swelling and limited motion of joint with deviation of mandible

- Conservative (complete) surgical management is treatment of choice
- Excellent prognosis, although recurrences may be seen; may rarely extend into cranial cavity and skull base

IMAGING

- Gold standard when diagnosis is suspected since it can visualize loose bodies at early stage and also evaluate disc condition and eventual extraarticular tissues involvement
- Excellent to define bony surfaces of articular joints but fails in detection of loose bodies when these are not yet calcified

MICROSCOPIC

- Consists of nodules of mature cartilage of varying cellularity within synovium and lying loosely in joint space
- Cartilage may appear atypical with hypercellularity, hyperchromasia, binucleated chondrocytes, and increased mitoses
- Calcification and ossification may be present

MR: Synovial Chondromatosis

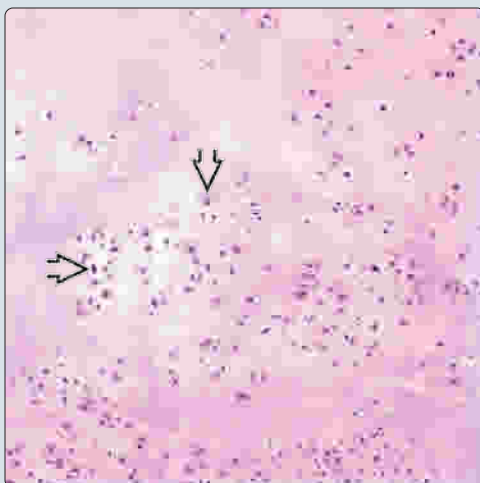


CT: Synovial Chondromatosis

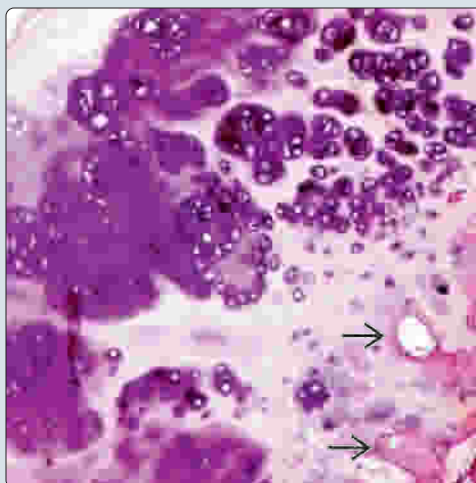


(Left) Sagittal T2WI MR shows hyperintense fluid surrounding the low-signal calcified loose bodies. MR is the gold standard when the diagnosis is suspected since it can visualize loose bodies at early stage and also evaluate disc condition and eventual extraarticular tissues involvement. (Right) Axial bone CT demonstrates multiple small calcified bodies diagnostic for synovial chondromatosis within the right temporomandibular joint just above the level of the head of the condyle.

Histology of Synovial Chondromatosis



Histology of Synovial Chondromatosis



(Left) The histology of synovial chondromatosis consists of nodules of mature cartilage of varying cellularity within the synovium and lying loosely in the joint space. The cartilage may appear atypical with hypercellularity, hyperchromasia, binucleated chondrocytes, and increased mitotic activity. (Right) Calcification and ossification may be present. Foci within the lobules can show endochondral ossification as a result of the normal evolution of cartilage.

Ceruminous Adenoma

KEY FACTS

TERMINOLOGY

- Benign glandular neoplasm of ceruminous glands of external auditory canal

CLINICAL ISSUES

- Rare neoplasm, < 1% of all external ear tumors
- Mean: 55 years; range: 12-85 years
- Must involve outer 1/3-1/2 of external auditory canal
- Mass and hearing changes, rarely painful
- Hearing loss (sensorineural and conductive), tinnitus

MICROSCOPIC

- Separated into 3 histologic types
 - Ceruminous adenoma; ceruminous pleomorphic adenoma; ceruminous syringocystadenoma papilliferum
- Well circumscribed but unencapsulated
- Dual cell population
- Inner luminal secretory cells with abundant granular, eosinophilic cytoplasm

- Luminal cells have decapitation (apocrine) blebbing or secretions

- Basal, myoepithelial cells at periphery adjacent to basement membrane
- Yellow-brown, ceroid, lipofuscin-like (cerumen) pigment granules in cytoplasm of luminal cells
- Background of dense, sclerotic fibrosis

ANCILLARY TESTS

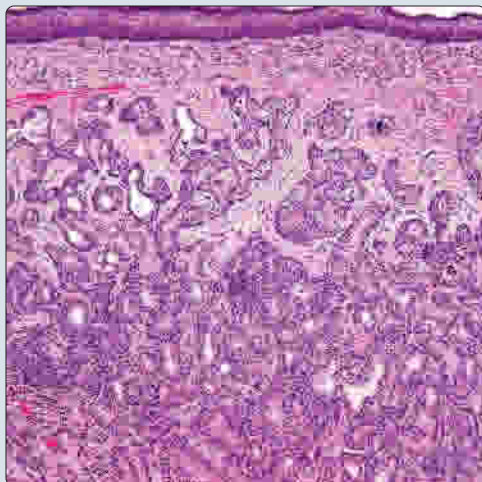
- Immunohistochemistry highlights dual cell population
- **Positive** luminal cells only: CK7
- **Positive** basal cells only: CK5/6, p63, S100 protein, and CD117 (predominantly)

TOP DIFFERENTIAL DIAGNOSES

- Ceruminous adenocarcinoma
- Neuroendocrine adenoma of middle ear
- Paraganglioma

(Left) Hematoxylin and eosin shows intact surface epithelium with glandular neoplastic proliferation in the stroma. There is a zone of separation. **(Right)** Hematoxylin and eosin shows numerous cerumen granules as yellow bodies within the cytoplasm of the luminal cells. There are only isolated basaloid cells in this proliferation.

Intact Surface Above Epithelial Neoplasm

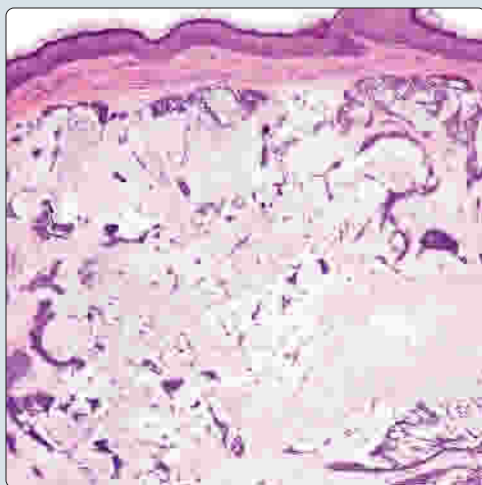


Cerumen (Ceroid) Granules

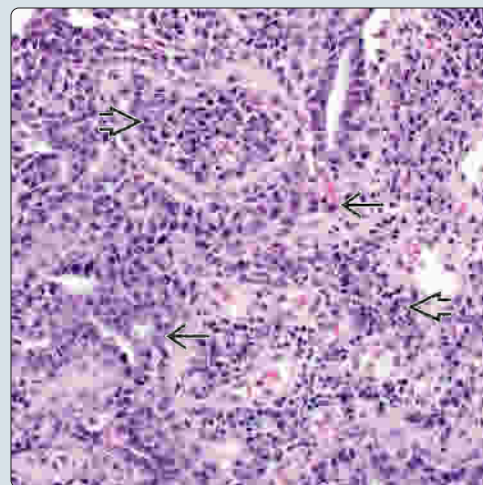


(Left) Hematoxylin and eosin shows myxochondroid matrix material with glandular cells below an intact surface in this ceruminous pleomorphic adenoma. **(Right)** The ceruminous glandular proliferation is set within an exophytic papillary frond architecture in this ceruminous syringocystadenoma papilliferum. Plasma cells are noted throughout.

Ceruminous Pleomorphic Adenoma



Ceruminous Syringocystadenoma Papilliferum



TERMINOLOGY

Synonyms

- Ceruminoma, ceruminal adenoma
- Apocrine adenoma, cylindroma

Definitions

- Benign glandular neoplasm of ceruminous glands of external auditory canal

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare neoplasm, < 1% of all external ear tumors
- Age
 - Mean: 55 years; range: 12-85 years
- Sex
 - Equal gender distribution

Site

- Must involve outer 1/3-1/2 of external auditory canal
- Posterior region affected slightly more commonly

Presentation

- Mass, sometimes with pain, tinnitus, nerve paralysis, hearing loss (sensorineural and conductive)
- May be asymptomatic

Treatment

- Surgical approaches
 - Complete surgical excision

Prognosis

- Excellent, although may have recurrences if incompletely excised

MACROSCOPIC

Size

- Mean: 1.2 cm; range: 0.5-2 cm

MICROSCOPIC

Histologic Features

- Tumors are separated into 3 histologic types
 - Ceruminous adenoma
 - Ceruminous pleomorphic adenoma
 - Ceruminous syringocystadenoma papilliferum
- Well circumscribed but unencapsulated
- Surface intact but may be "involved" rather than origin
- Glandular and cystic patterns
- Dual-cell population
 - Inner luminal secretory cells with abundant granular, eosinophilic cytoplasm
 - Yellow-brown, ceroid, lipofuscin-like (cerumen) pigment granules in cytoplasm of luminal cells
 - Basal, myoepithelial cells at periphery adjacent to basement membrane
 - Luminal cells have decapitation (apocrine) blebbing or secretions
- Low to moderate cellularity with limited pleomorphism
- Limited mitotic figures, if any, and never atypical forms

- Background of dense, sclerotic fibrosis in some cases
- Lacks necrosis
- Ceruminous pleomorphic adenoma
 - Chondromyxoid matrix material juxtaposed to epithelium and blended with it
- Ceruminous papillary cystadenoma papilliferum
 - Papillary projections lined by cuboidal to columnar cells
 - Heavy plasma cell investment

ANCILLARY TESTS

Immunohistochemistry

- Highlights biphasic tumor cells
 - **Positive** luminal and basal cells: Pancytokeratin, EMA
 - **Positive** luminal cells only: CK7
 - **Positive** basal cells only: CK5/6, p63, S100 protein, and CD117 (predominantly)
 - **Negative**: Chromogranin, synaptophysin, CK20

DIFFERENTIAL DIAGNOSIS

Ceruminous Adenocarcinoma

- Infiltrative, destructive growth
- Pleomorphism, including nucleoli; lacks ceroid pigment; usually show increased mitoses
- Necrosis, when present, helps with diagnosis

Neuroendocrine Adenoma of Middle Ear

- Neuroendocrine tumor with salt and pepper nuclear chromatin distribution
- Involves middle ear as primary site
- Biphasic appearance, lacking decapitation secretions and ceroid granules
- **Positive** with neuroendocrine markers (chromogranin, synaptophysin)

Paraganglioma

- Zellballen (nested) architecture
- Basophilic, slightly granular cytoplasm, often with isolated nuclear pleomorphism
- Paraganglia cells are **positive** with synaptophysin, chromogranin, CD56; sustentacular cells are S100 protein **positive**

Endolymphatic Sac Tumor

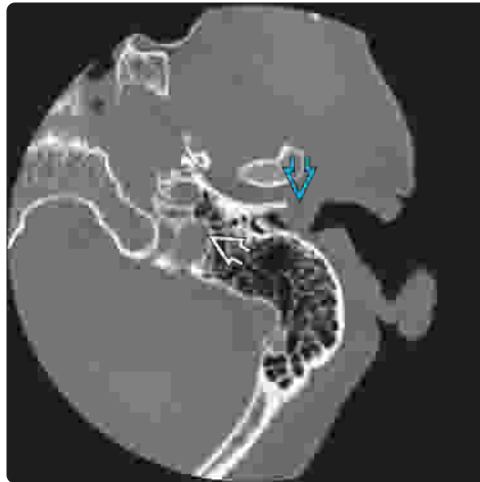
- Specific region in temporal bone (endolymphatic sac)
- Papillary architecture with cystic spaces lined by low cuboidal cells with pale to clear cytoplasm

SELECTED REFERENCES

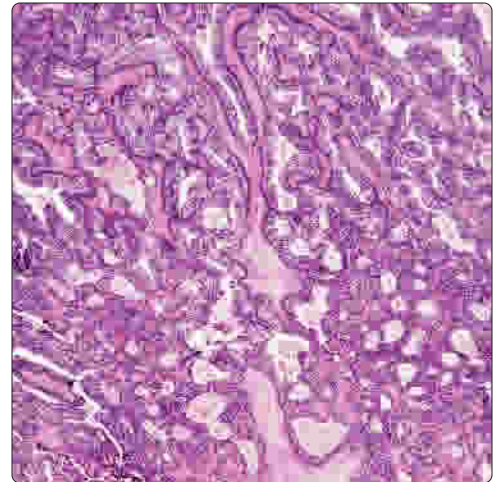
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External Auditory Canal Mass

(Left) CT demonstrates a mass within the external auditory canal that is filling the space. The middle ear is not involved. (Right) Hematoxylin and eosin shows a biphasic glandular proliferation with inner secretory cells. There is a fibrous connective tissue stroma between the glands.



Stromal Fibrosis Between Glands

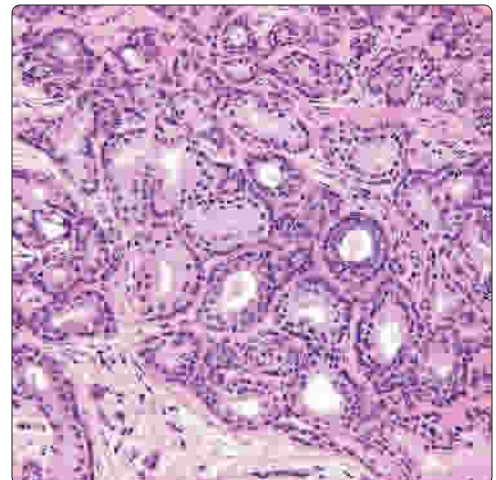


Biphasic Population: Inner Secretory Apocrine Cells

(Left) Hematoxylin and eosin shows brightly eosinophilic inner apocrine cells subtended by a basal cell proliferation, creating the biphasic appearance of a ceruminous adenoma. (Right) Hematoxylin and eosin shows a biphasic glandular proliferation with inner apocrine cells and basal myoepithelial cells, separated by fibrous connective tissue stroma.

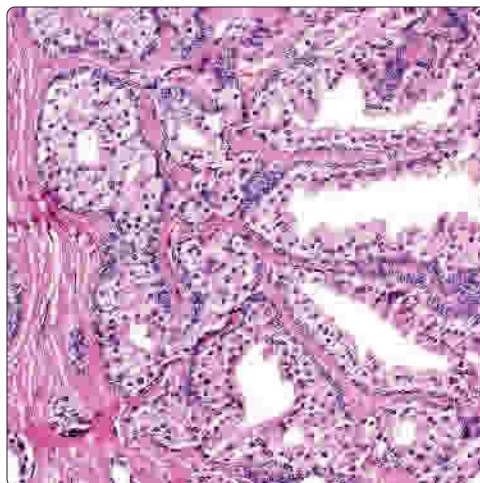


Glandular Appearance

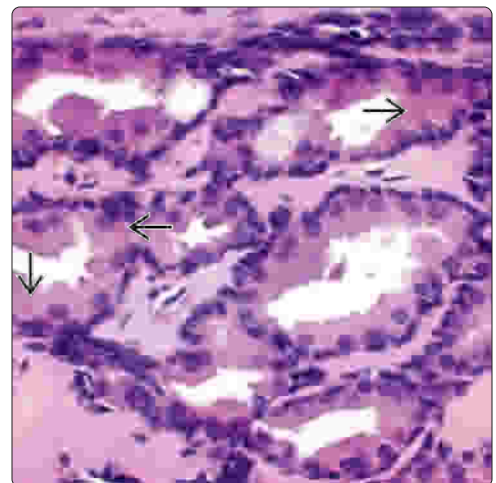


Columnar Cells With Decapitation Secretions

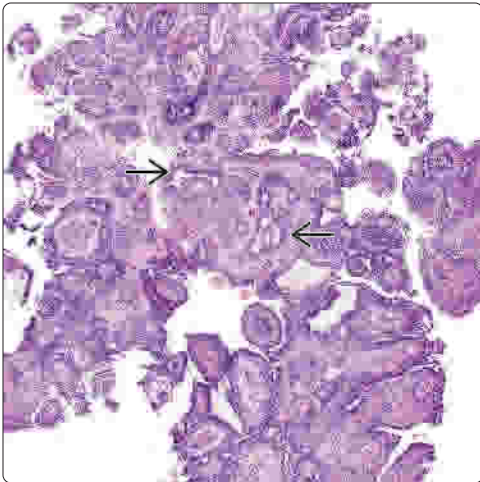
(Left) Intermediate-power magnification shows tall columnar secretory cells with apocrine-type snouts or decapitation secretions subtended by basal myoepithelial cells. Heavily collagenized stroma separates the glands. (Right) The yellow ceroid pigment granules can be quite difficult to identify in the luminal cells of ceruminous adenoma. Careful, high-power examination must be done to find them.



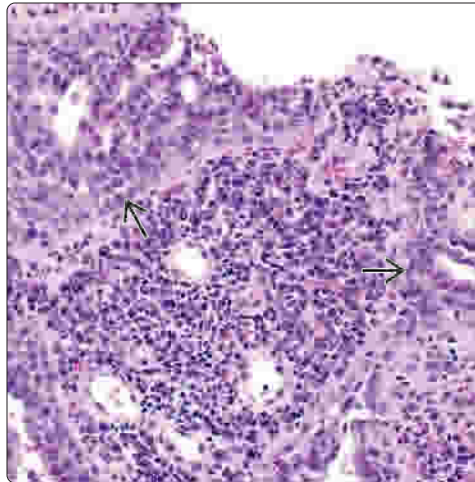
Ceroid Pigment Granules





Papillary Projections of Ceruminous Syringocystadenoma Papilliferum

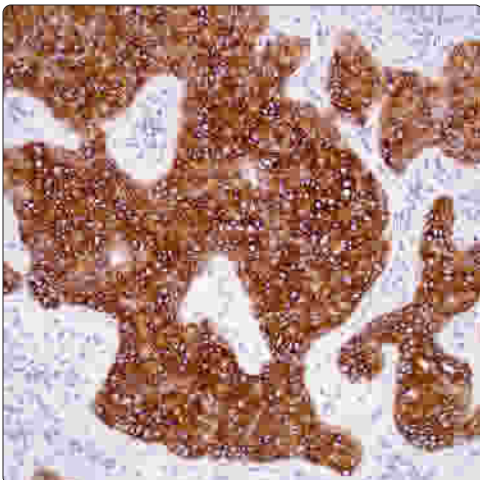


Plasma Cells in Ceruminous Syringocystadenoma Papilliferum

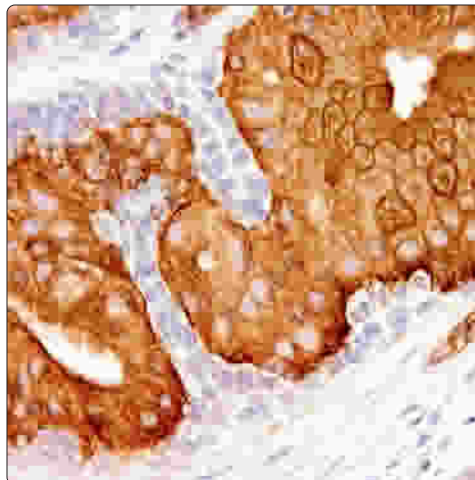


(Left) There are multiple papillary projections above the level of the epithelium in this ceruminous syringocystadenoma papilliferum. Glandular profiles  are seen towards the center or deeper tissues. **(Right)** The biphasic glandular epithelial components  surround plasma cells in the stroma of this ceruminous syringocystadenoma papilliferum.

Pancytokeratin Highlights Neoplastic Cells

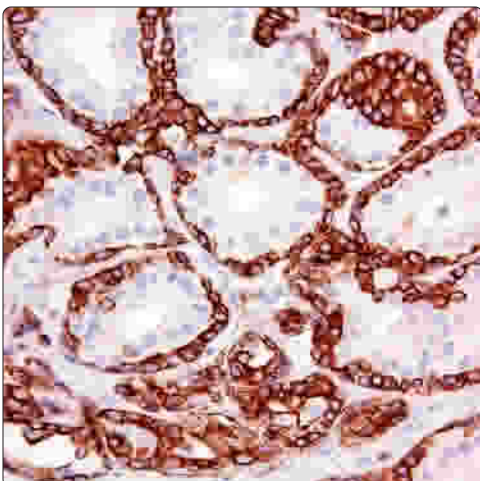


CK7 Highlights Luminal Cells



(Left) All of the neoplastic cells are reactive with pancytokeratin in ceruminous adenoma. However, it is easy to see a slight differential staining quality between the 2 cell types. **(Right)** CK7 shows strong cytoplasmic immunoreactivity of the luminal secretory cells and a lack of staining in the basal cells.

CK5/6 Highlights Basal Cells



Myoepithelial Cells Highlighted by S100 Protein



(Left) CK5/6 shows basal staining, highlighting the biphasic appearance of the tumor. This is a myoepithelial/basal marker in this particular setting. **(Right)** S100 protein shows nuclear and cytoplasmic immunoreactivity predominantly of the basal cells, although, there is background nonspecific staining (blush or tea staining) of the luminal secretory cells (perhaps related to endogenous biotin in these secretory cells).

Cholesteatoma

KEY FACTS

TERMINOLOGY

- Cholesteatoma, whether congenital or acquired, is proliferative
- Cystic keratinizing lesion of temporal bone, resulting in destruction of ossicular chain

ETIOLOGY/PATHOGENESIS

- Chronic inflammation plays critical role in stimulating epithelium to proliferate
- Releases cytokines, resulting in osteolysis of bone

CLINICAL ISSUES

- Propensity for older children and young adults
- Superior, posterior middle ear and petrous apex
- Chronic otitis media, foul smelling discharge, hearing loss
- Optimal treatment must be highly individualized
 - Complete surgical removal is treatment of choice although recurrences develop in ~ 20%

IMAGING

- High-resolution CT and DWI are complementary techniques
- Bone destruction usually present

MACROSCOPIC

- Multiple fragments of flaky, keratinaceous debris, associated with foul odor

MICROSCOPIC

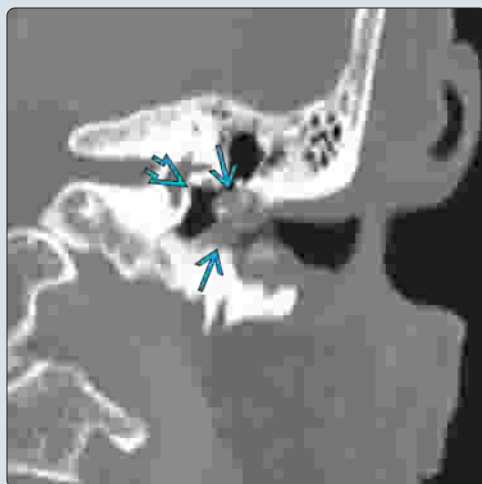
- Keratinous material (keratin flakes; dead, anucleate keratin squames)
- Stratified squamous epithelium with granular layer
- Inflamed stroma with fibrous connective tissue

TOP DIFFERENTIAL DIAGNOSES

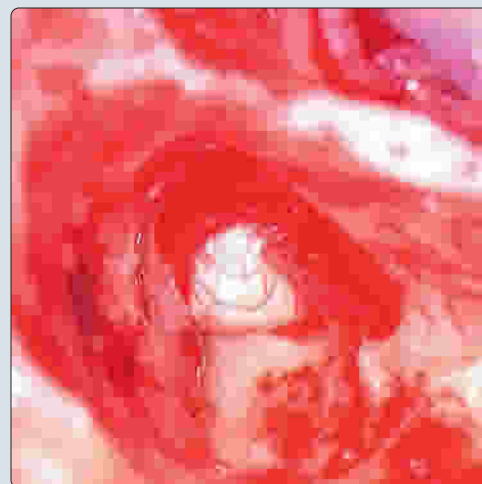
- Cholesterol granuloma
- Squamous cell carcinoma
- Otitis media
- Concurrent lesion

CT of Cholesteatoma

(Left) This image from a CT scan demonstrates inflammatory debris associated with bone destruction of the middle ear [B]. The ossicular chain is uninvolved [B]. (Right) An intraoperative photograph demonstrates a collection of keratin debris within the cavity. (Courtesy D. Cua, MD.)

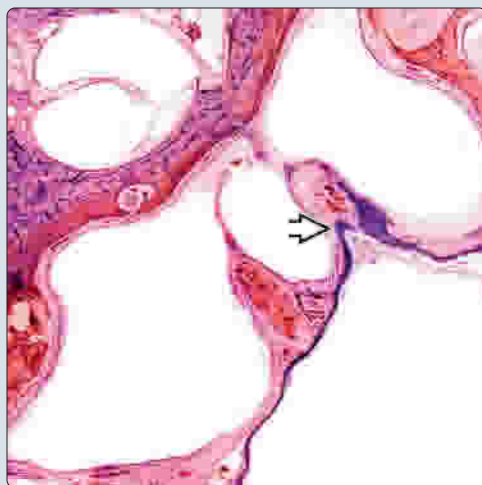


Intraoperative Image of Cholesteatoma

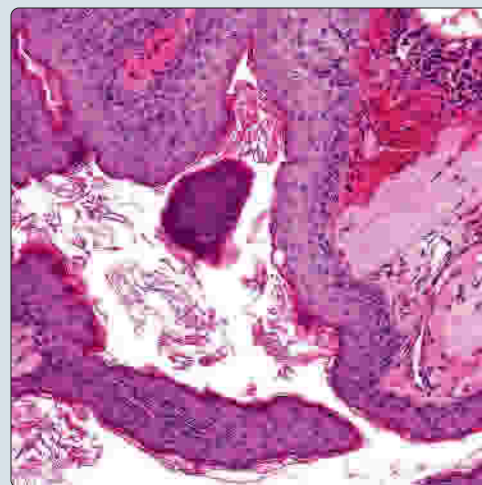


Congenital Cholesteatoma Whole Mount

(Left) Hematoxylin & eosin of a fetus temporal bone shows an area of retraction pocket formation [B]. This is 1 of the methods of cholesteatoma formation. (Courtesy L. Michaels, MD.) (Right) There are 3 elements that are usually required for a diagnosis of cholesteatoma: keratin debris, a prominent granular layer, and chronic inflammatory cells, all of which are seen in this image.



Keratin, Granular Layer, and Inflammation



TERMINOLOGY

Synonyms

- Glue ear, mastoiditis
- Keratosis obturans (incorrect)
 - Acute, severe pain due to accumulation of large plugs of desquamated keratin in **ear canal**, not **middle ear**

Definitions

- Proliferative, cystic keratinizing lesion of temporal bone, resulting in destruction of ossicular chain
- Congenital type
 - Develops behind normal and intact tympanic membrane, lacking eustachian tube dysfunction and otitis media
 - Arises from fetal epidermoid formations
- Acquired type
 - Defect (perforation) in tympanic membrane associated with inflammation
 - Results in proliferation of keratinizing epithelium
 - Via migration, immigration, squamous metaplasia, basal hyperplasia, retraction pocket (invagination), &/or trauma
 - Uncontrolled and dysregulated cell growth involving internal genomic &/or epigenetic alterations along with external stimuli, which produce extracellular and intracellular signal transduction cascades

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Chronic inflammation (usually from bacterial infection)
 - Plays critical role in stimulating epithelium to proliferate
 - Releases cytokines (tumor necrosis factor- α specifically but also receptor activator of nuclear factor κ B ligand and IL-1), producing collagenases, which results in osteolysis of bone

Congenital

- Small epidermoid formations occasionally develop during embryologic development
 - Found within anterosuperior quadrant of middle ear cleft epithelium
 - These give rise to congenital cholesteatoma if not resorbed (usually by end of 2nd year)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Common
- Age
 - Wide age range but propensity for older children and young adults (up to 4th decade)
- Sex
 - Equal gender distribution

Site

- Usually unilateral; may expand into adjacent structures
- Superior, posterior middle ear (acquired); anterior, superior middle ear (congenital); petrous apex

Presentation

- Transtympanic endoscopy through perforation made by laser-assisted myringotomy helps with diagnosis
- Long history of severe chronic otitis media, often refractory to therapy
- Hearing loss due to destruction of ossicular chain (conductive not sensorineural)
- Otagia, otorrhea, foul-smelling aural discharge, headaches
- Perforation of tympanic membrane (acquired form)
- Petrous bone cholesteatoma
 - Facial nerve involved in ~ 95%; facial paralysis
 - Vestibular dysfunction, vomiting, vertigo, and tinnitus
- Rarely, intracranial complications; when present, emergent management required
- Congenital cholesteatoma patients tend not to have otitis media or hearing loss

Treatment

- Options, risks, complications
 - Cholesteatomas are invasive, aggressive, and recurrent lesions, resulting in considerable morbidity if not managed correctly
 - Optimal treatment is controversial but needs to be highly individualized
 - Urgent surgery necessary if facial nerve dysfunction, vertigo, or severe headaches are present
 - Complications include fistula, sigmoid sinus erosion, cranial nerve dysfunction, meningitis, and epidural or brain abscess
- Surgical approaches
 - Complete surgical removal
 - Modified radical (ossicles remain) or radical (stapes remains) mastoidectomy
 - Attic compartments require adequate aeration
- Drugs
 - Early antibiotic treatment of otitis media and associated inflammatory conditions may decrease chance of developing cholesteatoma

Prognosis

- This reactive and osteolytic process can be aggressive and recidivistic
 - Recurrences in about 20% of cases
 - Increased risk of recurrence if patient is < 20 years, marked ossicular chain erosion/destruction, polypoid mucosal disease, and extensive disease
- Congenital cholesteatoma patients tend to do better
 - Require early detection to achieve best result

IMAGING

Radiographic Findings

- Preoperative radiology essential to identify landmarks and extent of disease
- Soft tissue mass displacing ossicles medially
- Bone destruction usually present
- High-resolution CT and non-echo-planar DWI are complementary techniques

MR Findings

- Best in characterizing expansile & destructive lesions of petrous apex

- High-resolution scanning techniques can define precise spatial relationships of middle and inner ear structures
- Excellent in postoperative evaluation of completeness of removal, development of complications or recurrence
- Detects involvement of meninges and veins (sigmoid sinus, jugular)
- Prolongation of both T1 and T2 signals

CT Findings

- Highlights small abnormalities of thin and complex bony structures
- Precise extent of bone erosion
- Identifies fistulization through tegmen tympani or posterior wall of temporal bone

MACROSCOPIC

General Features

- Gray-white to yellow irregular mass behind tympanic membrane
- Multiple fragments of flaky, keratinaceous debris, foul odor

Sections to Be Submitted

- Submit all tissue to confirm diagnosis

MICROSCOPIC

Histologic Features

- Epithelium behaves like wound-healing process without any inherent genetic instability
- Name is misnomer because it is not clonal neoplasm and does not contain cholesterol
 - However, it destroys local tissues and can recur
- Normal middle ear epithelium is cuboidal or columnar glandular epithelium: Squamous epithelium is abnormal
- 3 components required for diagnosis
 - Keratinous material (keratin flakes; dead, anucleate keratin squames)
 - Stratified squamous epithelium with granular layer (derived from external auditory canal)
 - Inflamed stroma with fibrous connective tissue
- Epithelium is keratinizing, stratified squamous epithelium without atypia, tends to be atrophic, and lacks rete pegs
- Epithelium lines cystic space filled with exfoliated anucleated squames
- Inflammatory component is usually lymphocytes, plasma cells, histiocytes, and mast cells
- Concurrent disorders include cholesterol granuloma, otic polyp, tympanosclerosis, acquired encephalocele, and neuroendocrine adenoma of middle ear

ANCILLARY TESTS

Immunohistochemistry

- Ki-67 (MIB-1) and ErbB-2 are increased in cases that are more biologically aggressive
- Keratin 16 strong expression (marker of hyperproliferative keratinocytes)

In Situ Hybridization

- FISH shows extra copy of chromosome 7
 - Correlates with proliferation activity and is seen in cases that are more clinically aggressive

DIFFERENTIAL DIAGNOSIS

Cholesterol Granuloma

- Elongated clefts (spaces) left by cholesterol crystals dissolved in processing
- Foreign body giant cell reaction with inflammation
- Hemosiderin-laden macrophages with granulation tissue
- May be identified concurrently with cholesteatoma

Squamous Cell Carcinoma

- Squamous epithelial cells are pleomorphic/atypical
- Lack of maturation or polarity
- Have dyskeratosis and keratin pearl formation
- Increased mitotic figures, including atypical forms

Otitis Media

- Lacks proliferative squamous epithelium and anucleated squames

Concurrent Lesion

- Identify any concurrent lesion, i.e., neuroendocrine adenoma of middle ear, paraganglioma, squamous cell carcinoma

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CT of Middle Ear Cholesteatoma

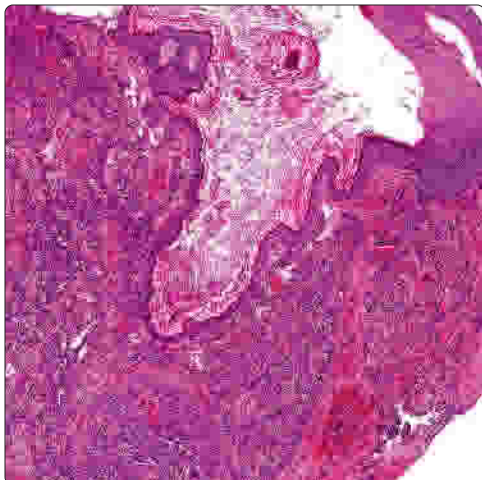


Cystic Cavity of Cholesteatoma

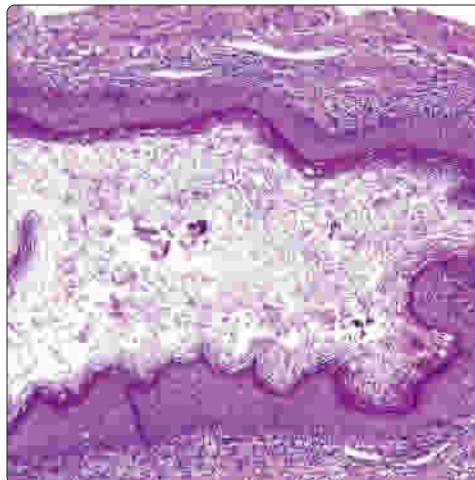


(Left) This high-resolution CT study demonstrates a nearly complete filling of the middle ear by a soft tissue density mass. There is no significant bone destruction or remodeling. **(Right)** Hematoxylin & eosin shows squamous epithelium with keratin debris and inflamed fibrous connective tissue. The squamous epithelium is not thickened and shows no atypia although there is a prominent granular layer.

Neuroendocrine Adenoma of Middle Ear and Cholesteatoma

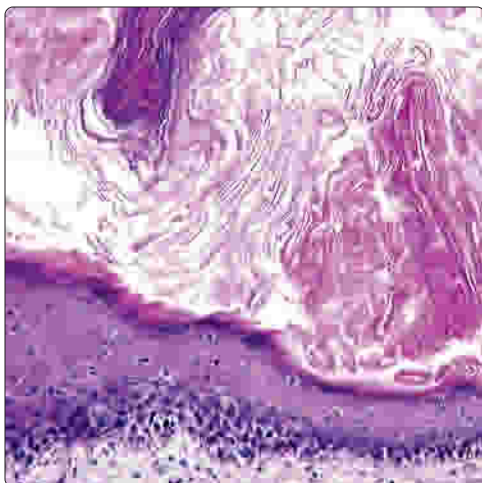


Proliferative Squamous Epithelium

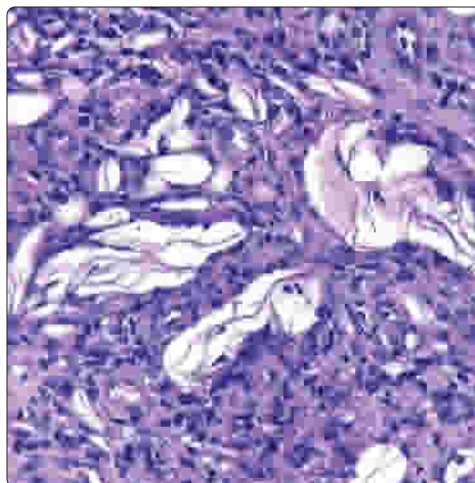


(Left) There are frequently associated findings with a cholesteatoma, which in this case are represented by a neuroendocrine adenoma of middle ear. It is not uncommon to have more than one diagnosis in middle ear cases. **(Right)** Hematoxylin & eosin shows a proliferation of squamous epithelium with associated inflammation and keratin debris. The epithelium is sometimes corrugated or verruciform.

Keratin Debris and Granular Cell Layer



Giant Cell Reaction to Keratin



(Left) Hematoxylin & eosin shows squamous epithelium with keratin debris and fibrous connective tissue. There is an easily identified granular cell layer although this is not always the case. **(Right)** Keratin flakes are frequently identified in association with inflammation and foreign body giant cell reaction. This is not a cholesterol granuloma; however, the lesions can sometimes be concurrent.

KEY FACTS

TERMINOLOGY

- Benign neoplasm of middle ear showing both cytomorphologic and immunohistochemical neuroendocrine differentiation, mucin-secreting differentiation

CLINICAL ISSUES

- Most common tumor of middle ear
- Average: 45 years; range: 20-80 years
- Unilateral conductive hearing loss is most common presenting symptom
 - Tinnitus, discharge, otitis media, ear pressure, fullness
- Complete excision (including ossicles) is treatment of choice

IMAGING

- Mass in middle ear with intact tympanic membrane, lacking changes of chronic otitis media

MICROSCOPIC

- Unencapsulated and infiltrative growth
- Variable architectural patterns: Glandular, trabecular, cords, festoons, single cells
- Ducts show dual cell population
 - Inner, luminal, flattened eosinophilic cells
 - Basal, cuboidal-columnar cells
- Delicate, fine, salt and pepper nuclear chromatin
- Gland lumen may have secretions
- Desmoplastic stroma is common

ANCILLARY TESTS

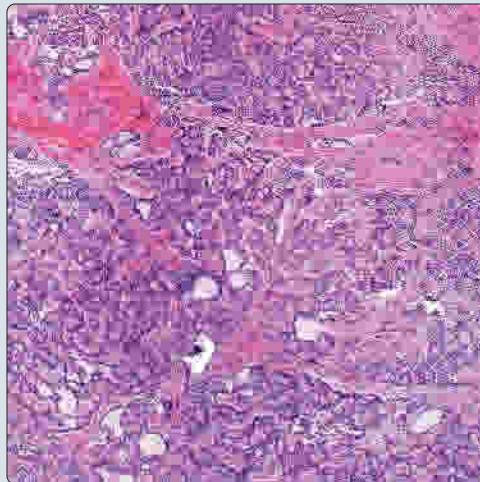
- Keratin, CK7, CK5/6, p63, chromogranin, synaptophysin, HPP, ISL1

TOP DIFFERENTIAL DIAGNOSES

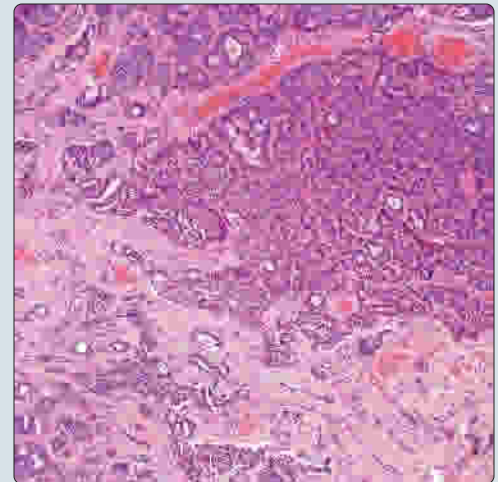
- Paraganglioma, ceruminous adenoma, metastatic adenocarcinoma, meningioma

Multiple Patterns of Growth

(Left) There are multiple different patterns of growth in this neuroendocrine adenoma of the middle ear (NAME). There are glandular profiles, solid sheets, pseudorosettes, and fibrosis dissecting between the epithelial islands. **(Right)** In general, neuroendocrine adenomas of middle ear are unencapsulated and infiltrative tumors, showing a variety of architectures, as seen in this low magnification: Glandular, tubular, trabecular, cords, and single cell architecture.

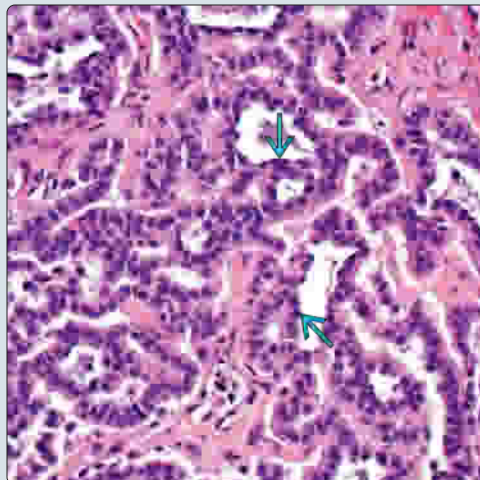


Pseudoinfiltrative Growth

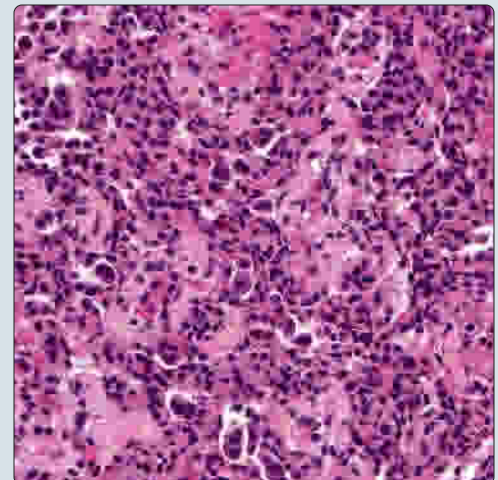


Gland and Duct-Like Structures

(Left) Duct-like structures show back to back configuration, with a dual population of inner, luminal, flattened eosinophilic cells and basal, cuboidal-columnar cells with finely granular cytoplasm. **(Right)** There are numerous plasmacytoid cells in this field of a NAME. There is background fibrosis. There is limited atypia, although many of the nuclei show a more coarse, heavy nuclear chromatin distribution.



Plasmacytoid Cells



TERMINOLOGY

Abbreviations

- Neuroendocrine adenoma of middle ear (NAME)

Synonyms

- Middle ear adenoma (MEA)
- Carcinoid tumor

Definitions

- Benign glandular neoplasm of middle ear showing both cytomorphologic and immunohistochemical neuroendocrine and mucin-secreting differentiation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon (< 2% of ear tumors)
- Age
 - Average: 45 years; range: 20-80 years
- Sex
 - Equal gender distribution

Site

- Middle ear cavity
- May extend into adjacent structures
 - External auditory canal (via tympanic membrane)
 - Mastoid bone &/or eustachian tube

Presentation

- Unilateral hearing loss
 - Conductive hearing loss if ossicular chain involved
- Ear pressure or fullness
- Tinnitus
- Otitis media, discharge, bleeding
- Otoscopic exam
 - Pink soft tissue mass behind intact tympanic membrane
 - Dark brown-reddish fluid behind ear drum
- No serologic evidence of neuroendocrine function

Treatment

- Options, risks, complications
 - Facial nerve paralysis &/or paresthesias may be due to mass effect rather than invasion of nerves
- Surgical approaches
 - Complete surgical excision, including ossicular chain, to prevent recurrence
 - Reconstruction required
- Radiation
 - No role for radiation in treatment of this benign tumor

Prognosis

- Excellent long-term clinical outcome
- Recurrences develop if incompletely excised
 - ~ 15% of patients, specifically if ossicular chain is not removed with tumor
- **No** metastatic potential

IMAGING

General Features

- Best study is axial and coronal bone CT without contrast

- Soft tissue mass within well-pneumatized mastoid, usually lacking features of chronic otitis media
- Nondestructive mass lesion within middle ear
 - Involves middle ear cavity proper (mesotympanum)
 - No bone invasion, but ossicular encasement and bone remodeling (if large or present for long duration)
 - Usually shows irregular margination
 - Tympanic membrane is intact
- May appear indistinguishable from cholesteatoma

MACROSCOPIC

General Features

- Ossicular chain is usually affected, but tissue tends to peel away from bony structures
- Soft, rubbery, and unencapsulated
- Usually multiple white, yellow, gray-tan to reddish tissue fragments

Size

- Usually < 1 cm, limited by anatomic confines of middle ear

MICROSCOPIC

Histologic Features

- Surface origin is absent
- Unencapsulated and infiltrative growth, with possible bone involvement
- Moderate cellularity
- Variable architectures: Glandular, trabecular, cords, festoons, single cells
- Duct-like structures with back-to-back configuration
- Ducts show dual cell population
 - Inner, luminal, flattened eosinophilic cells
 - Basal, cuboidal-columnar cells with finely granular cytoplasm
 - **No** myoepithelial cell layer
- Eccentrically placed (plasmacytoid) round to oval nuclei
- Delicate, fine, salt and pepper nuclear chromatin distribution
- Small nucleoli
- Mitotic figures absent to infrequent
- Gland lumen may have secretions
- Fibrotic to desmoplastic stroma is common
- Pleomorphism, necrosis and perineural/lymph-vascular space invasion all absent
- Cholesteatoma may be concurrently present but is not etiologically related

ANCILLARY TESTS

Histochemistry

- Mucinous material identified in gland lumen (or rarely intracytoplasmic) with PAS and Alcian blue

Immunohistochemistry

- Both epithelial and neuroendocrine markers **positive**
 - CK-PAN, CK7, CK5/6, CAM5.2, p63
 - Chromogranin, synaptophysin, CD56, NSE
- Differential staining may be seen
 - Inner luminal cells with CK7
 - Outer basal cells with neuroendocrine markers

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CK-PAN	Positive	Cytoplasmic	All tumor cells
CK8/18/CAM5.2	Positive	Cytoplasmic	All tumor cells
CK7	Positive	Cytoplasmic	Highlights inner (luminal) cells within glandular spaces
CK5/6	Positive	Cell membrane & cytoplasm	Predominantly abluminal cells
p63	Positive	Nuclear	Abluminal cells only
Chromogranin-A	Positive	Granular	Tends to be greater in basal layer
Synaptophysin	Positive	Cytoplasmic	Tends to be greater in basal layer
NSE	Positive	Granular	
CD56	Positive	Cytoplasmic	
ISL1	Positive	Nuclear	Nearly all tumor cells
HPP	Positive	Granular	Usually basal cells
S100	Negative		
GFAP	Negative		
Actin-sm	Negative		
TTF-1	Negative		

- Peptides and transcription factors **positive**: Human pancreatic polypeptide (HPP), islet-1 (ISL1), serotonin, glucagon
- **Negative**: S100 protein, SMA, TTF-1, pax-8

Electron Microscopy

- 2 distinct cell types
 - Type A: Apical dark cells with elongated microvilli and secretory mucus granules
 - Type B: Basal cells with cytoplasmic, solid, dense-core neurosecretory granules
- Transitional forms with features of both cell types uncommon

DIFFERENTIAL DIAGNOSIS

Paraganglioma

- Zellballen architecture, although sometimes cells are compressed
- Isolated pleomorphism, with basophilic granular cytoplasm
- **Positive**: Paraganglia cells with chromogranin, synaptophysin, CD56; sustentacular cells: S100 protein

Ceruminous Adenoma

- Involves outer ear canal
- Biphasic appearance: Inner luminal and outer basaloid cells
- Decapitation apocrine secretions and cerumen
- **Positive**: Epithelial markers; S100 protein & SMA (basal cells)
- **Negative**: Neuroendocrine markers

Metastatic Adenocarcinoma

- Tumors tend to be destructively infiltrative
- Moderate to marked pleomorphism
- Usually increased mitotic count
- Clinical history combined with targeted immunohistochemistry helps differentiate

Meningioma

- Whorled, meningothelial pattern, frequently with psammoma bodies
- Intracellular cytoplasmic inclusions
- **Positive**: Delicate, sparse EMA reaction
- **Negative**: Neuroendocrine markers

DIAGNOSTIC CHECKLIST

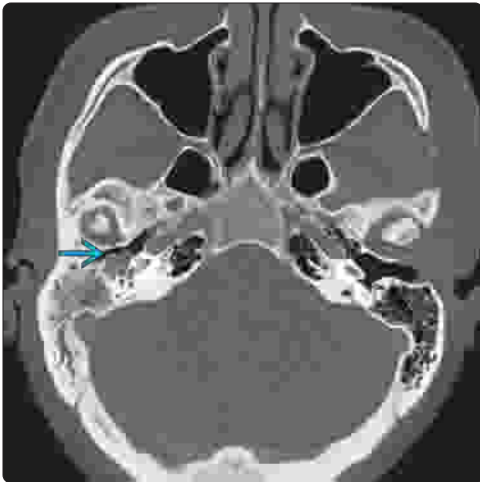
Pathologic Interpretation Pearls

- Pseudoinfiltrative pattern of tumor is characteristic
- Gland and duct-like pattern with secretions are common

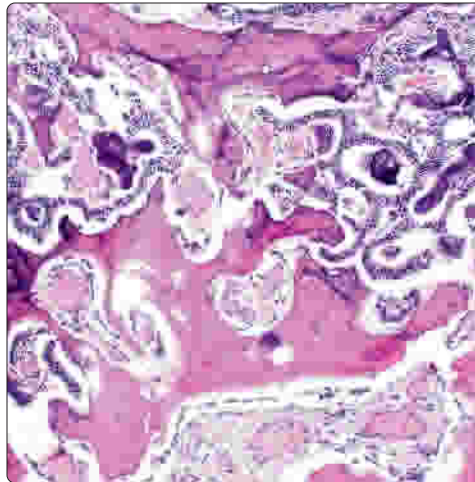
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CT of Middle Ear Mass

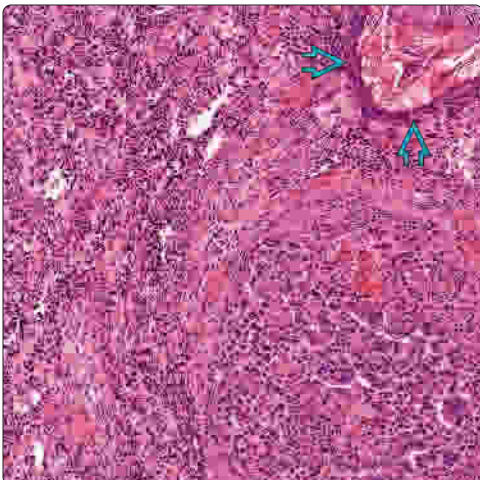


Bone Infiltration of Stapes

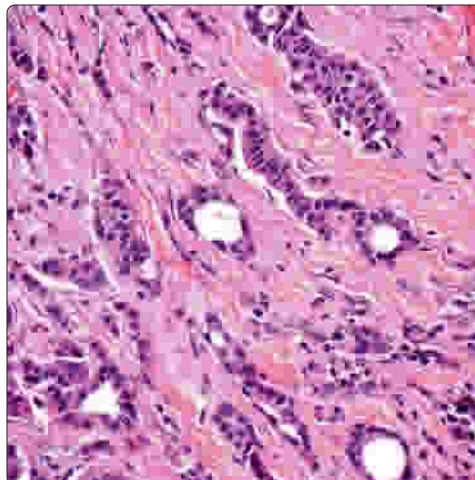


(Left) There is a tumor involving the middle ear, showing encasement of the ossicles [E], but lacking destructive bony growth. Ossicles need to be removed to avoid recurrence. (Right) The bony spicules are remodeled with ribbons of glandular-type epithelium noted in the interstices of one of the ossicles. This tumor had been present for many years.

Multiple Patterns and Cholesteatoma

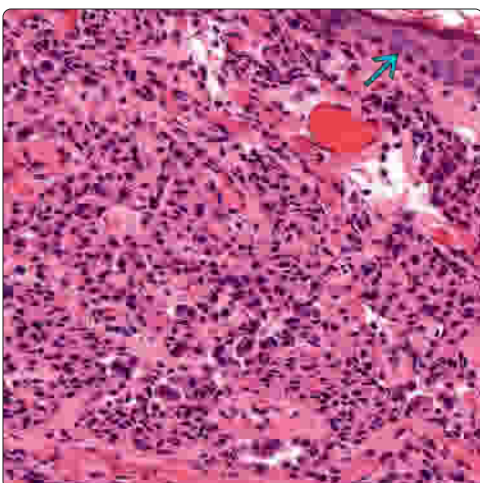


Fibrotic Stroma With Glandular Epithelium

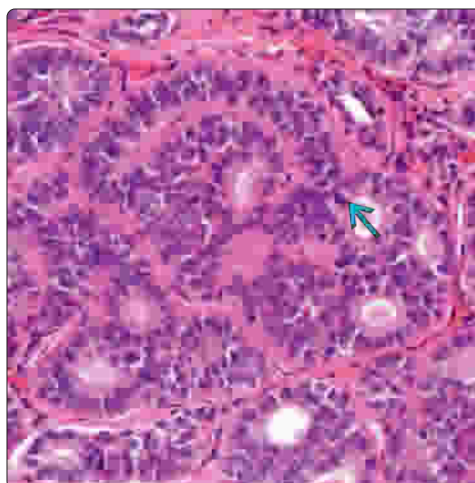


(Left) This tumor shows a large number of different patterns within a single low-power field. A solid pattern shows pseudopapillary degenerative-type changes. There is a concurrent cholesteatoma [E]. This is not an uncommon associated finding. (Right) The infiltrative pattern of small cells in single file or small nests to glandular patterns can mimic or simulate an infiltrating adenocarcinoma. The stroma is fibrotic and collagenized but is not desmoplastic.

Moderately Cellular Tumor



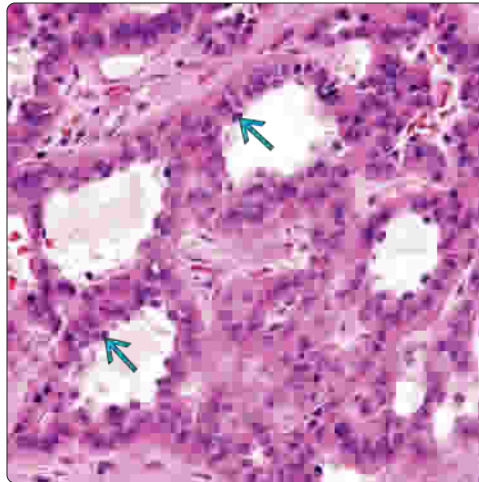
Glandular Profiles With Secretions



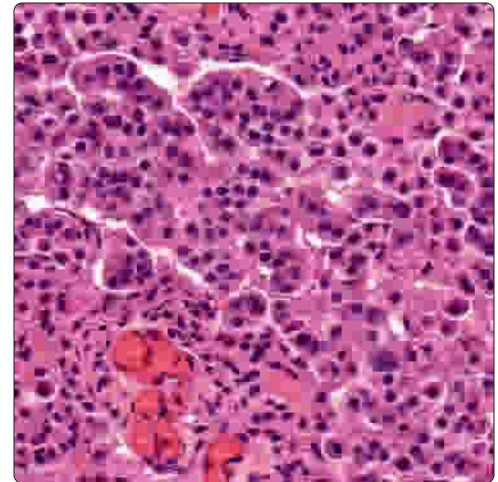
(Left) There is a moderate cellularity to this tumor, immediately below an intact surface epithelium [E] that is not associated with the tumor. A number of different patterns are seen. (Right) Glandular or cribriform patterns can be seen in neuroendocrine adenomas of middle ear. The stroma surrounds the structures. There are concretions within the lumen of many of the glandular profiles. The cells are monotonous in this field, with delicate, salt & pepper nuclear chromatin distribution. Mitotic figure is noted [E].

Biphasic Glandular Profile

(Left) A biphasic glandular profile is seen in this tumor. There is an attenuated inner luminal layer with surrounding basal, cuboidal epithelial elements. This biphasic appearance is easily highlighted with immunohistochemistry. (Right) A certain degree of variability is often present in these tumors. Here, the cytoplasm surrounds eccentrically placed round to oval nuclei with hyperchromatic chromatin distribution. These cells have a plasmacytoid appearance.

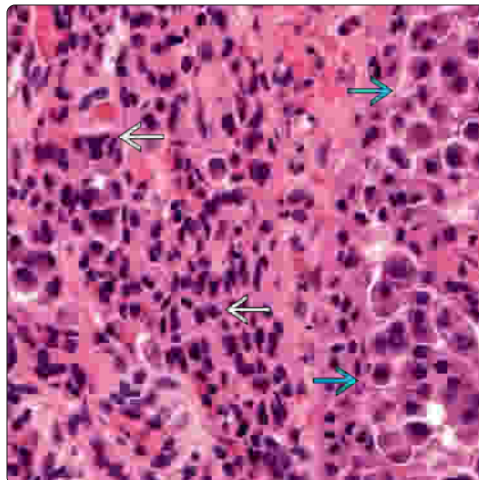


Solid Growth of Small Plasmacytoid Cells

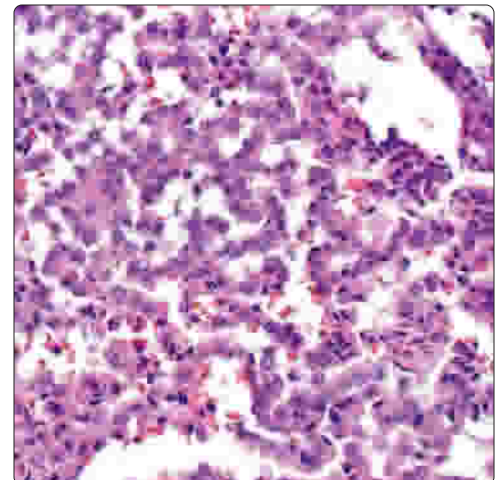


Abrupt Transitions Between Patterns

(Left) Abrupt transitions between various patterns is the norm for this tumor type. A solid pattern is immediately adjacent to a more infiltrative, single cell pattern. (Right) This cellular tumor shows a glandular pattern, but a festoon arrangement is noted throughout. The nuclei are round and regular with delicate chromatin distribution. Extravasated erythrocytes are focally noted in this tumor.

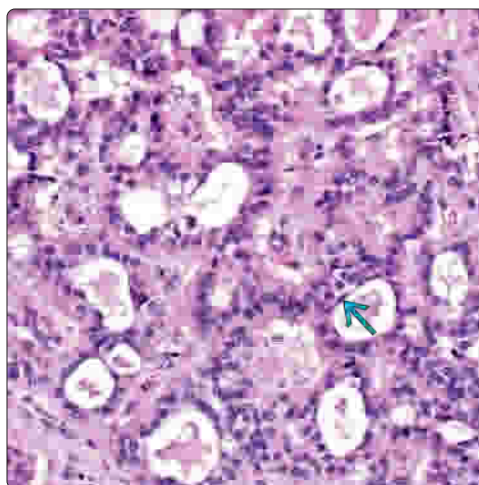


Glandular Pattern

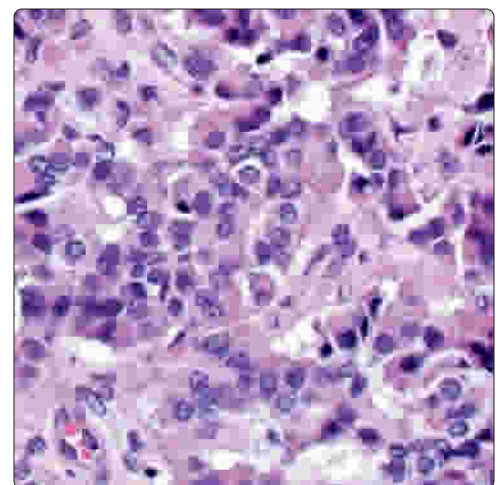


Inner Lining Cells With Secretions

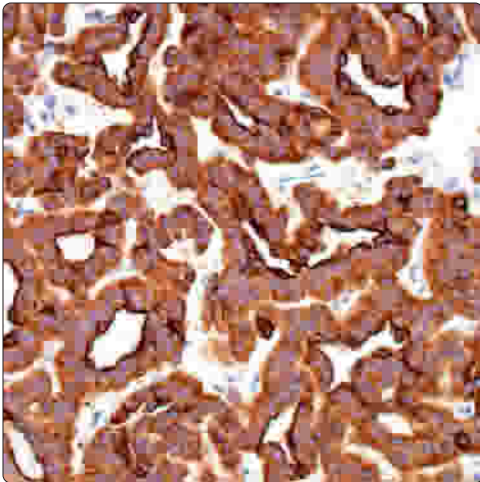
(Left) The inner lining cells within the glandular profiles can be very scant and sparse, often requiring immunohistochemistry to highlight. (Right) The neoplastic cells show a plasmacytoid appearance, with eosinophilic cytoplasm surrounding round nuclei with delicate, salt and pepper nuclear chromatin distribution.



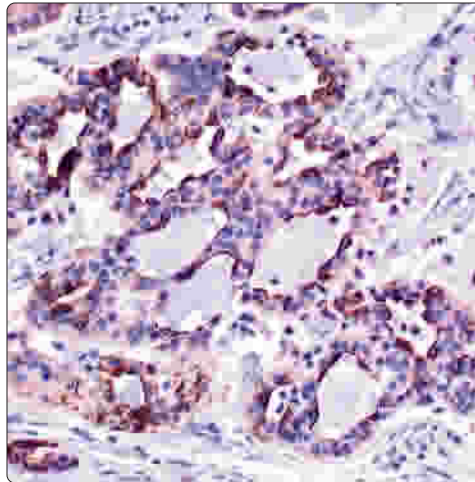
Plasmacytoid Cells With Neuroendocrine Nuclei



Strong but Differential CK-PAN Immunoreactivity

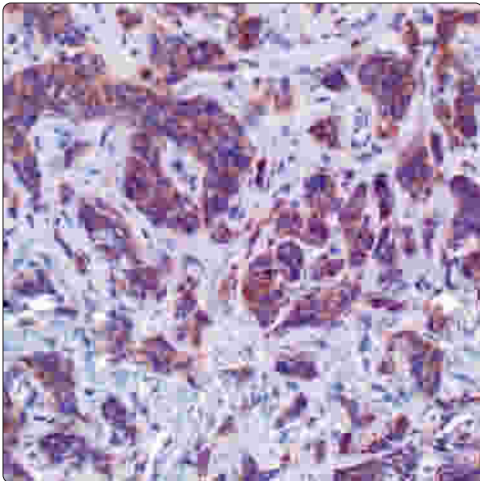


CK7 Highlights Inner Luminal Cells

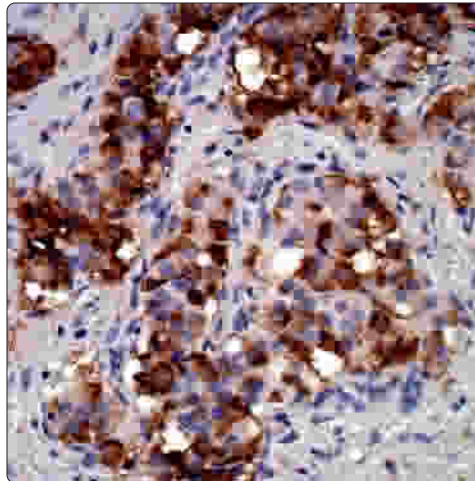


(Left) Immunohistochemical evaluation is helpful in confirming the diagnosis. In this case, there is strong and diffuse keratin immunoreactivity. However, the inner lining cells are highlighted with a darker, heavier chromogen deposition. (Right) CK7 preferentially reacts with the inner lining cells of the glandular profiles. This marker can be useful in highlighting the biphasic nature of the neoplasm, with the basal cells staining more strongly with neuroendocrine markers.

Synaptophysin Highlights Neoplastic Cells

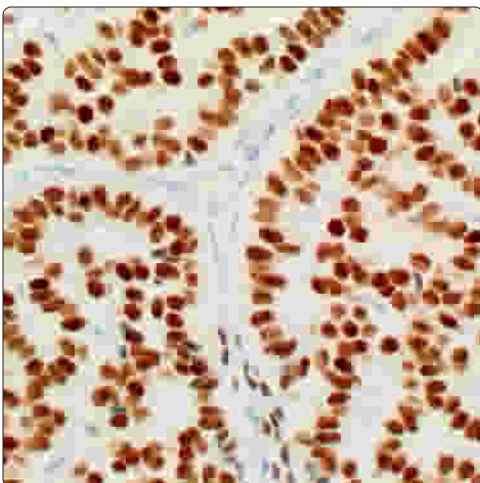


Chromogranin Highlights Most Neoplastic Cells

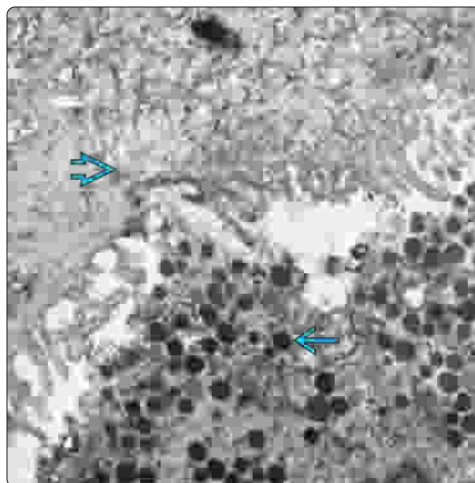




(Left) Nearly all of the neoplastic cells in this pseudoinfiltrative field are positive with synaptophysin, highlighting the neuroendocrine nature of the neoplasm. (Right) Chromogranin highlights many neoplastic cells, but a number of cells are nonreactive, representing the inner, luminal, or glandular cells. There is a more granular reaction with chromogranin when compared to synaptophysin or CD56.

ISL-1 Strongly Stains Nuclei



Dense-Core Neurosecretory Granules (EM)



(Left) Several transcription factors and peptides are positive in NAME, with this illustration showing strong and diffuse nuclear reaction with ISL-1, a neuroendocrine transcription factor usually seen in pancreatic tissue. (Right) EM highlights the 2 cell types of a NAME. Type A: Apical dark cells with elongated microvilli and secretory mucus granules . Type B: Basal cells with cytoplasmic, solid, dense-core neurosecretory granules .

Jugulotympanic Paraganglioma

KEY FACTS

TERMINOLOGY

- Synonyms: Glomus jugulare, glomus tympanicum
- Neoplasm arising from paraganglia in vicinity of jugular bulb or medial cochlea promontory

CLINICAL ISSUES

- 10% multicentric, 10% bilateral, 10% familial
- Female >> male (5:1) in sporadic tumors
- 90% of tumors of jugular foramen are paraganglioma
- Pulsatile tinnitus
- Hearing loss (conductive)
- Do not biopsy: Very vascularized and will bleed
- Presurgical embolization for reduced bleeding
- 15% mortality due to proximity of vital anatomic structures

IMAGING

- CT: Bone only without contrast shows mass with flat base on cochlear promontory

- T1WI MR: Multiple black dots in tumor indicate high-velocity flow voids
- Octreotide or MIBG scintigraphy helps with occult or familial tumors

MICROSCOPIC

- Clustered, zellballen architecture
- Richly vascularized stroma, sometimes with fibrosis
- Small to intermediate cells with ample granular, basophilic cytoplasm

ANCILLARY TESTS

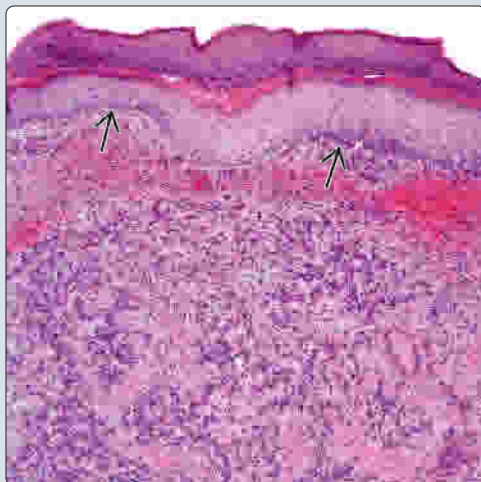
- Neuroendocrine markers: CD56, chromogranin, synaptophysin; S100 protein sustentacular cells

TOP DIFFERENTIAL DIAGNOSES

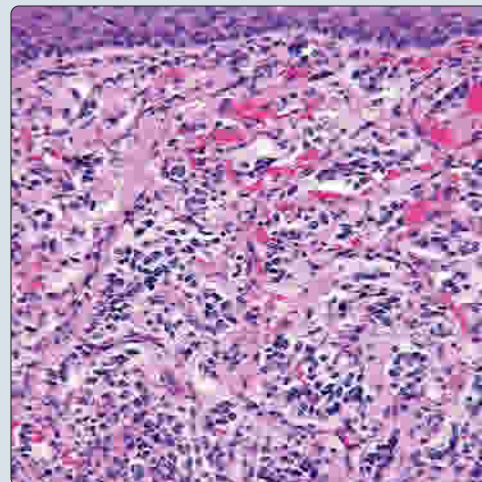
- Schwannoma
- Meningioma
- Neuroendocrine adenoma of middle ear

Subepithelial Paraganglioma

(Left) The squamous lining is intact with a subepithelial proliferation of paraganglia cells. Note the hemorrhage and fibrosis in this disrupted lesion. **(Right)** H&E shows an intact squamous epithelium (from the external auditory canal [EAC]) subtended by a nested neoplastic proliferation associated with a rich vascularized network and fibrous connective tissue.

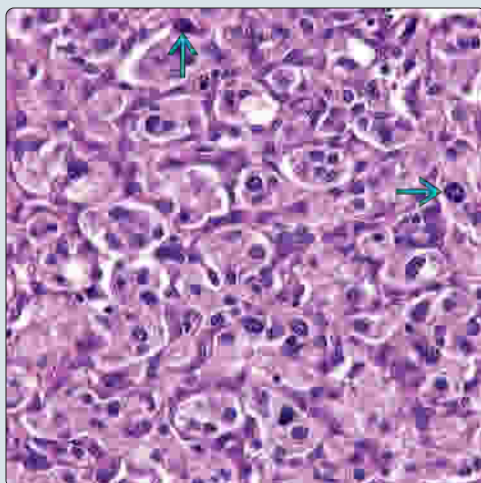


Nested or Zellballen Pattern

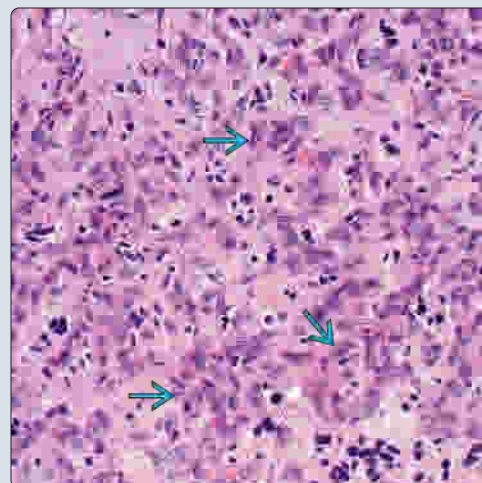


Well-Defined Nests

(Left) The zellballen arrangement gives a characteristic nesting or alveolar appearance to the neoplasm. There is focal nuclear pleomorphism. The neoplasm is supported by a delicate vascular plexus. **(Right)** There is a well-developed fibrosis that partially obscures the paraganglia neoplasm. These cells are arranged in vague nests, which are difficult to discern on standard H&E stained material.



Fibrosis Partially Obscures Proliferation



TERMINOLOGY

Abbreviations

- Glomus tympanicum paraganglioma (GTP)
- Glomus jugulotympanicum paraganglioma (GJP)

Synonyms

- Glomus tympanicum or glomus jugulare
- Jugulotympanic chemodectoma
- Glomus in pathology is usually applied to smooth muscle vascular tumor of nail bed soft tissue

Definitions

- Neoplasm arising from paraganglia in vicinity of jugular bulb or medial cochlea promontory
 - Radiographically and surgically glomus tympanicum (GTP) and glomus jugulotympanicum (GJP) paragangliomas are distinctive and unique
 - However, they are identical by pathology parameters; these clinical terms will be used for nonpathology findings

ETIOLOGY/PATHOGENESIS

Cell of Origin

- Arises from paraganglia
 - Along inferior tympanic nerve (Jacobson nerve)
 - Around jugular foramen
 - Auricular branch of CNX (Arnold nerve)
- Chemoreceptor cells are derived from neural crest
 - Respond to changes in blood oxygen and carbon dioxide levels

CLINICAL ISSUES

Epidemiology

- Incidence
 - Most common tumor of middle ear (GTP)
 - Most common tumor of jugular foramen (GJP) (~ 90%)
 - Together, GTP and GJP account for 80% of head and neck paragangliomas
 - ~ 30% familial
 - 10% rule: Multicentric (carotid body, adrenal pheochromocytoma), bilateral, pediatric, malignant
- Age
 - Range: 10-85 years; mean: 6th decade
- Sex
 - Female >> male (5:1) for sporadic tumors
 - Male > female for inherited/familial tumors

Site

- GTP: Middle ear surface of promontory
 - Anterior inferior quadrant of tympanic membrane
- GJP: Jugular foramen
 - Wall of jugular bulb

Presentation

- Pulsatile tinnitus (~ 90% of patients)
- Hearing loss (~ 50% of patients): Conductive rather than sensorineural
- Vascular retrotympanic mass
- Pain

- Facial nerve paralysis
- If familial or syndrome: Autosomal dominant trait with genomic imprinting

Treatment

- Options, risks, complications
 - Do not biopsy: Very vascularized and will bleed
 - Slow-growing but locally destructive tumor, which can be watched in older patients
 - Presurgical embolization for reduced bleeding
 - Complications: 2/3 of patients experience postoperative cranial neuropathy, while others may have recurrence or CSF leak
- Surgical approaches
 - GTP: Tympanotomy for small lesions or mastoidectomy for larger lesions
 - GJP: Infratemporal fossa approach (Fisch type A)
- Radiation
 - Gamma knife radiosurgery can be effective
 - May work for localized tumors
 - Palliative in poor surgical candidates or older patients

Prognosis

- Excellent overall outcome
- Aggressive clinical behavior is seen in ~ 8-10% of cases
- 15% mortality due to proximity of vital anatomic structures
- Distant metastases are exceedingly rare

IMAGING

General Features

- Radiographs accurately define location, size, extent
- Glomus tympanicum
- CT: Bone only without contrast: Mass with flat base on cochlear promontory (GTP); mass in jugular foramen with **permeative-destructive** change in adjacent bone (GJP)
- MR: Enhancing mass (GTP); T1WI: Multiple black dots in tumor indicate high-velocity flow voids from feeder arterial branches (GJP)
- Angiography: Allows for preoperative embolization by identifying blood supply
- Octreotide or MIBG scintigraphy helps with occult or familial tumors
- PET with F-18 FDG: Avid uptake by tumor cells

MACROSCOPIC

General Features

- Fragmented due to anatomic restrictions
- Irregular, reddish firm masses
- Variegated cut surface with blood and degeneration
- Tympanic membrane usually intact
- Can be widely invasive, filling apical portion of petrous temporal bone and middle ear

Size

- Variable, but difficult to measure due to fragmentation
- GTP: Range: 0.3-2.5 cm; GJP: Range: 2-6 cm

MICROSCOPIC

Histologic Features

- Clustered, zellballen architecture

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
Chromogranin-A	Positive	Cytoplasmic	Paraganglia cells
Synaptophysin	Positive	Cytoplasmic	Paraganglia cells
NSE	Positive	Cytoplasmic	Paraganglia cells
CD56	Positive	Cell membrane	Paraganglia cells
S100	Positive	Nuclear & cytoplasmic	Sustentacular supporting cells
GFAP	Positive	Cytoplasmic	Sustentacular supporting cells
CK-PAN	Negative		
CEA-M	Negative		
SDHB	Positive	Nuclear	Expression lost in malignant tumors

- Richly vascularized stroma, sometimes with fibrosis
- Poorly encapsulated or circumscribed, often infiltrative
- Moderately cellular
- Cyst formation, hemorrhage, and hemosiderin-laden macrophages common
- Small to intermediate cells with ample granular, basophilic cytoplasm
- Nuclei are round to focally irregular and enlarged
- Delicate to coarse nuclear chromatin
- Multinucleated cells are uncommon
- Mitotic figures vanishingly rare

ANCILLARY TESTS

Cytology

- Fine-needle aspiration is usually contraindicated, as procedure may provoke hypertensive crisis or result in significant bleeding
- Smears are usually hypercellular, with cells arranged singly or in small groups, often creating pseudorosette
- 3 cell types are interspersed throughout smear
 - Cells are small- to moderate-sized polygonal-shaped with delicate, granular cytoplasm
 - Spindle cells with ample cytoplasm and elongated nuclei
 - Large, strap-like cells with large, eccentric nuclei with prominent nucleoli

Immunohistochemistry

- Neuroendocrine markers and supporting sustentacular framework

Genetic Testing

- Germline mutations in several genes encoding various subunits of succinate-ubiquinone oxidoreductase gene (SDH)
 - These enzymes are in mitochondrial respiratory chain complex II
 - *PGL1-PLG4* encodes SDH subunits A-D on 11q, 1q, and 1p
- Inactivating mutations in *SDHB*, *SDHC*, and *SDHD* genes cause hereditary paraganglioma
- Genetic counseling and testing for *SDHX*, *VHL*, *NF1*, and *RET* genes should be offered to all patients with paraganglioma

DIFFERENTIAL DIAGNOSIS

Schwannoma

- Spindle cells with alternating cellular and hypocellular areas, perivascular hyalinization
- **Positive:** S100 protein, SOX10

Meningioma

- Whorled, epithelioid proliferation with intranuclear cytoplasmic inclusions and possible psammoma bodies
- **Positive:** EMA

Neuroendocrine Adenoma of Middle Ear

- Multiple growth patterns, with glandular appearance, and salt and pepper nuclear chromatin distribution
- **Positive:** Keratin and neuroendocrine markers

STAGING

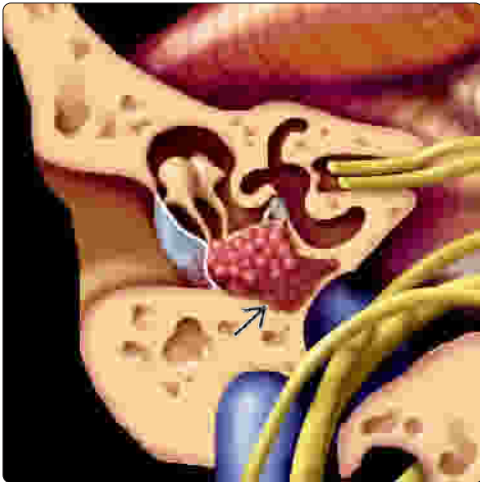
Glasscock-Jackson Classification

- Type I: Tumor limited to cochlear promontory
- Type II: Tumor filling middle ear space
- Type III: Tumor filling middle ear and extending into mastoid air cells
- Type IV: Tumor filling middle ear, extending into mastoid bone &/or external auditory canal, or extending anterior to carotid artery

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Graphic of GTP

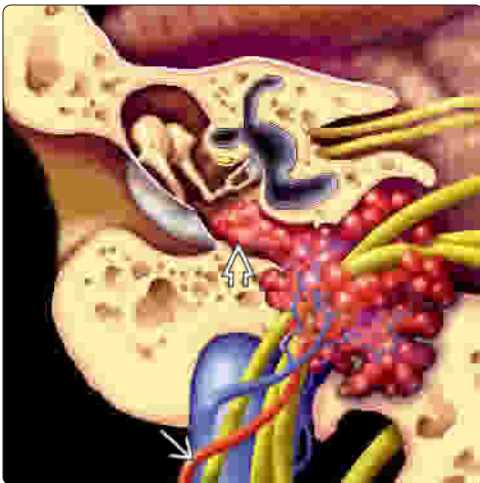


CT of Large Destructive Glomus

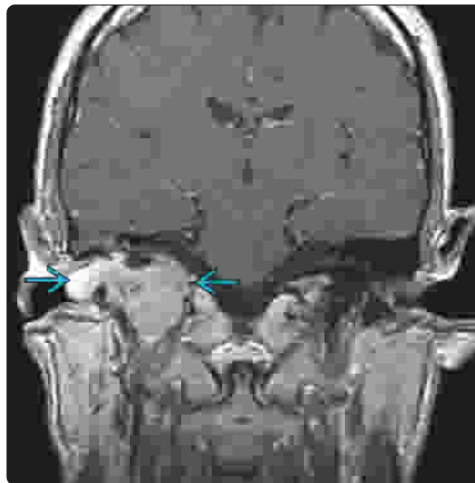


(Left) Coronal graphic shows a highly vascular glomus tympanicum paraganglioma (GTP) expanding off the cochlear promontory, filling the middle ear cavity, and subtly expanding into the bony floor [X]. (Right) There is a large bone destructive mass centered within the temporal bone [X], which shows a moth-eaten appearance. The specific type of tumor may not be determined by radiology alone.

Graphic of Large GJP

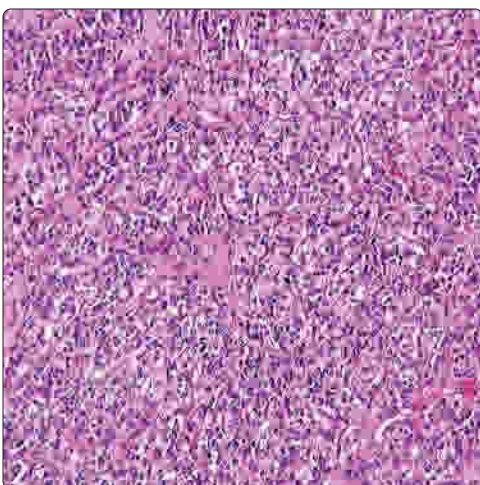


MR of Large Glomus Jugulare

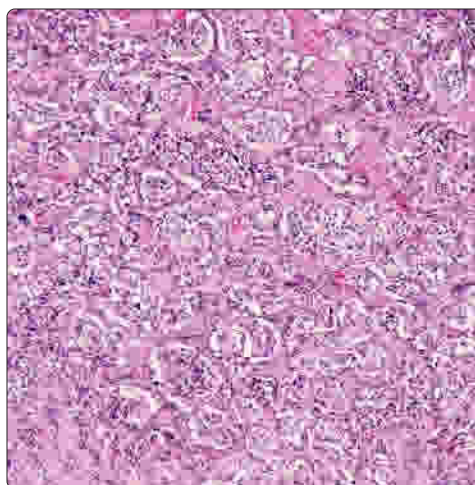


(Left) Coronal graphic shows a glomus jugulare paraganglioma (GJP) centered in the jugular foramen with superolateral extension into the middle ear [X]. The ascending pharyngeal artery [X] is feeding this tumor and could be used for embolization during angiography. (Right) Coronal T1 MR post contrast shows an enhancing lesion [X] filling and destroying the area of the temporal bone. This is quite characteristic of a highly vascular tumor, such as a paraganglioma.

Cellular Nested Architecture



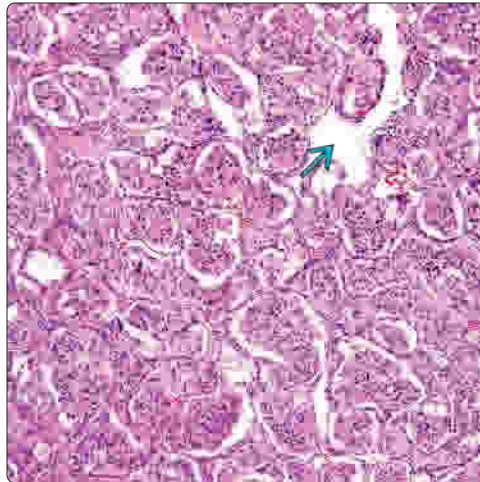
Fibrovascular Stroma



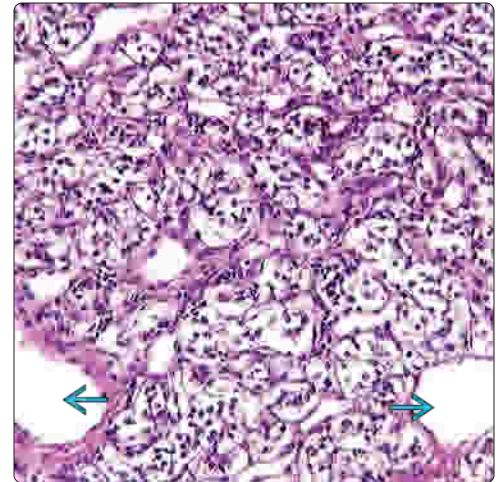
(Left) There is a clustering and a zellballen architecture to this paraganglioma. Note the richly vascularized stroma, focally associated with fibrosis. The tumor is cellular. (Right) Paragangliomas have similar features but show quite significant variability between cases. Here the zellballen architecture is highlighted by a more well-developed fibrotic fibrovascular stroma. The cells show abundant cytoplasm.

(Left) This cellular tumor shows a nested to focally trabecular architecture. There is focal cyst formation. The cells are small with a syncytial architecture. The cytoplasm is granular and eosinophilic. **(Right)** H&E shows a rich vascular plexus with associated nests of tumor. The cytoplasm is difficult to appreciate and appears cleared in this tumor. There are many larger vessels in this neoplasm.

Trabecular and Nested Pattern

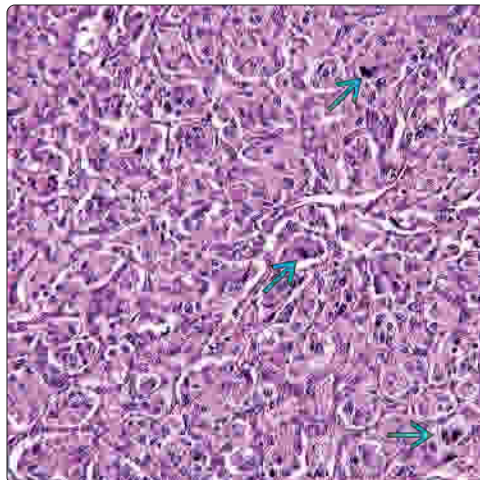


Loose Vascular Plexus

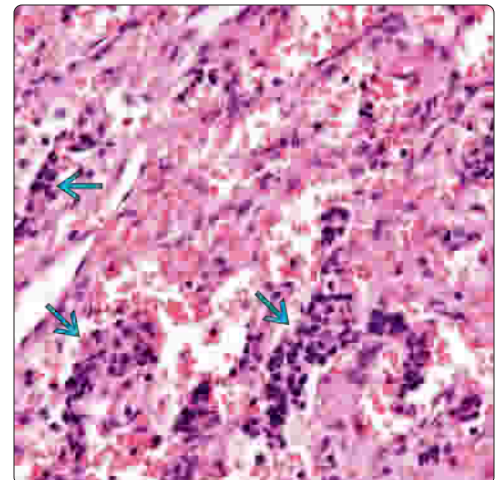


(Left) The clustered growth of this tumor shows a vague meningotheelial-type growth pattern. The sustentacular supporting framework is limited as is the fibrosis. There is still focal nuclear pleomorphism. **(Right)** The tumors are richly vascularized, and so it is not uncommon to have hemorrhage or bleeding into the tumor. In this case, there are only small isolated nests of neoplastic cells, while the dominant finding is the hemorrhage or degeneration.

Clustered Nests With Focal Pleomorphism

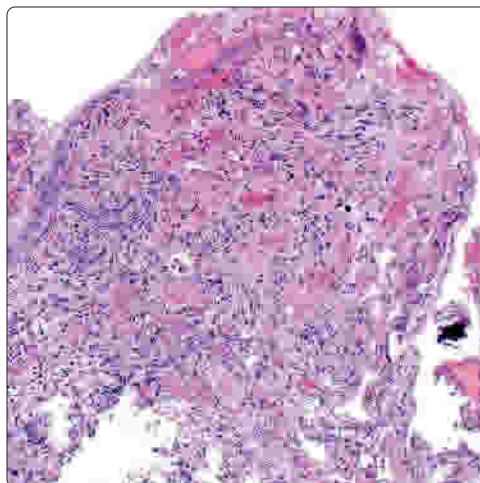


Hemorrhage Within Stroma

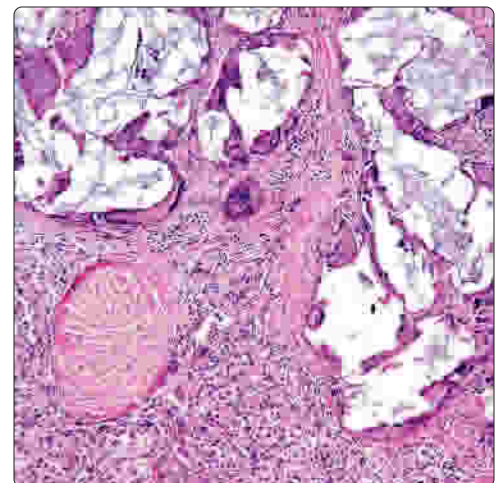


(Left) Heavy electrocautery artifact is a frequent problem with vascular tumors, such as a paraganglioma. Therefore, the neoplastic cells may show electrothermal artifacts, obscuring the true neoplastic nature of the lesion. **(Right)** Angiography is used to identify the feeder vessel to the tumor, allowing for embolization, which results in decreased hemorrhage during surgery and possible tumor infarction. Note the foreign embolic material.

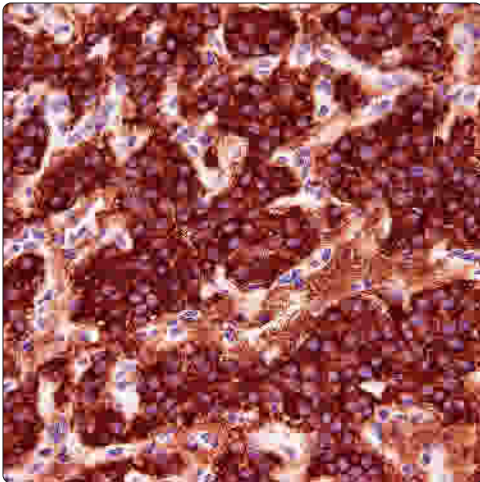
Hyalinization and Electrocautery Artifacts



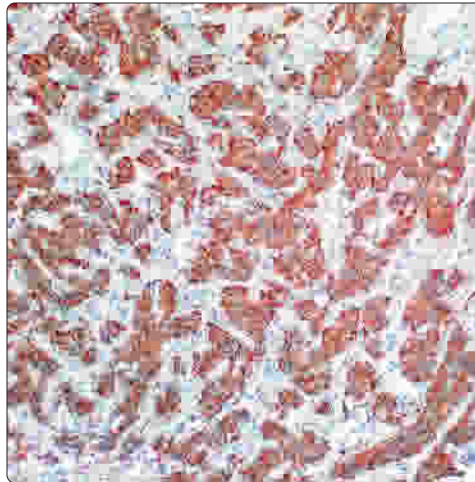
Embollic Material Within Paraganglioma



Strong, Diffuse Chromogranin Reactivity

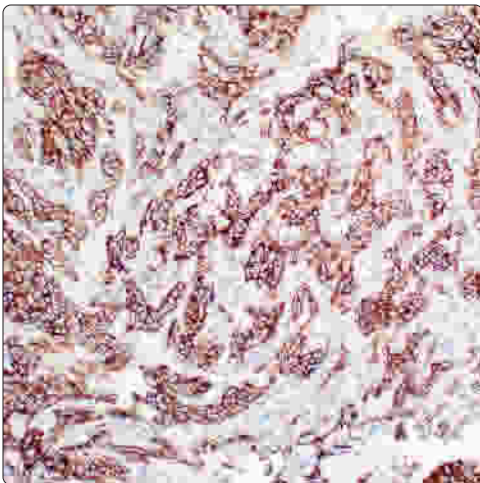


Synaptophysin Reaction

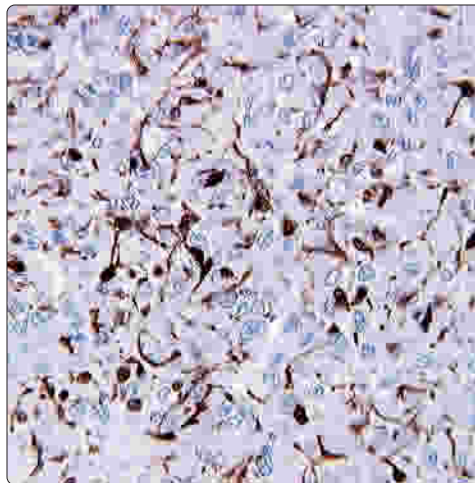


(Left) Neuroendocrine markers will highlight the paraganglia cells. Chromogranin is often the strongest and most diffuse stain, showing a granular cytoplasmic reaction. (Right) There is a delicate but well-developed strong reaction in the neoplastic cells with synaptophysin. There is often an accentuation along the membranes (the location of the presynaptic vesicles).

CD56 Membrane Reaction

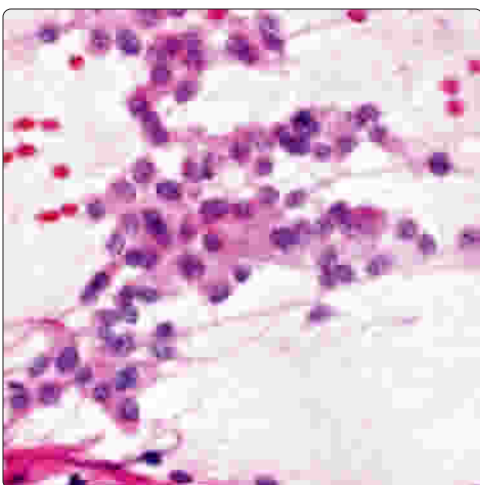


Sustentacular S100 Protein Reaction

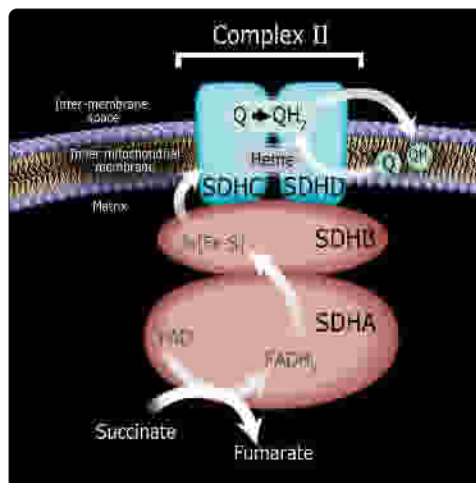


(Left) The neoplastic cells are highlighted by a strong membrane to cytoplasmic reaction with CD56, a neuroendocrine-related marker that can be seen in paraganglioma. (Right) The supporting sustentacular framework is highlighted with S100 protein. It is a discontinuous staining on a 2-dimensional section. Both the nucleus and the delicate wisps of cytoplasm will be highlighted with the stain. GFAP gives a similar result.

Fine-Needle Aspiration of Paraganglioma



Graphic of SDH Complex



(Left) Cellular smear shows cells arranged in small groups. Usually 3 cell types are present in varying degree. Here, there are small- to moderate-sized polygonal-shaped cells with delicate, granular cytoplasm. (Courtesy L. Layfield, MD.) (Right) Graphic of part of the mitochondrial respiratory chain complex II shows the relationship between the succinate-ubiquinone oxidoreductase subunits (SDHA-SDHD). Inactivating mutations result in hereditary paraganglioma.

Schwannoma (Acoustic Neuroma)

KEY FACTS

TERMINOLOGY

- Benign nerve sheath tumor arising within internal auditory canal (IAC) or intralabyrinthine

CLINICAL ISSUES

- Most common neoplasm of temporal bone
- Most common in 5th-6th decades
- Unilateral progressive hearing loss in 90% of patients
 - Sensorineural loss, **not** conductive
- Tinnitus (80% of patients): High-pitched ringing or steam kettle-type hissing
- Craniotomy with middle fossa or suboccipital approach
- Stereotactic-guided gamma knife or fractionated stereotactic radiotherapy
- Excellent overall prognosis with low recurrence potential

IMAGING

- Cerebropontine angle; posterior fossa intracanalicular mass
- Funnel-shaped widening of internal auditory canal

MACROSCOPIC

- Eccentric, globular mass, frequently attached to a cranial nerve

MICROSCOPIC

- Cellular (Antoni A) closely packed spindle cells
- Microcystic or loosely reticular Antoni B areas
- Palisaded nuclei (Verocay body)
- Cells are fusiform with buckled nuclei and fibrillary cytoplasm
- Medium-sized vessels with perivascular hyalinization

ANCILLARY TESTS

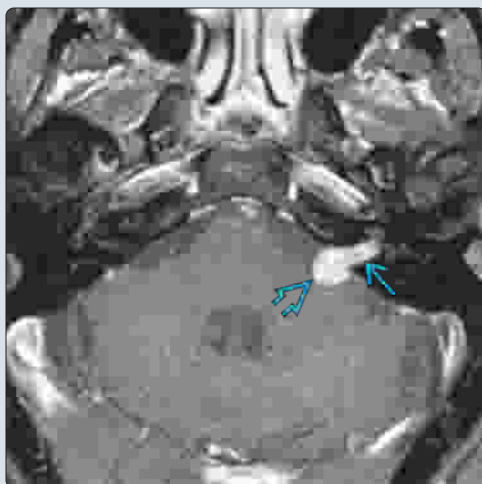
- Strong S100 protein and SOX10 immunoreactivity

TOP DIFFERENTIAL DIAGNOSES

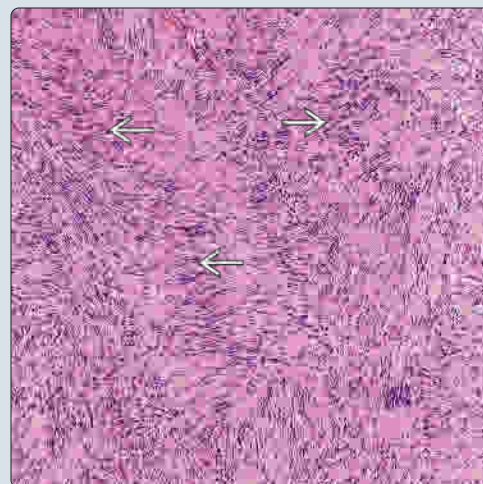
- Meningioma, neurofibroma, solitary fibrous tumor, malignant peripheral nerve sheath tumor

MR of Acoustic Neuroma

(Left) Axial contrast-enhanced T1 MR shows an enhancing acoustic neuroma filling the left internal auditory canal (IAC) and extending out into the cerebellopontine angle (CPA). Note the typical ice cream cone (IAC portion) and ice cream (CPA portion) morphology. (Right) A low-power view demonstrates the interlacing short fascicles of spindled cells. There is palisading to the nuclei, a feature quite characteristic of schwannoma.

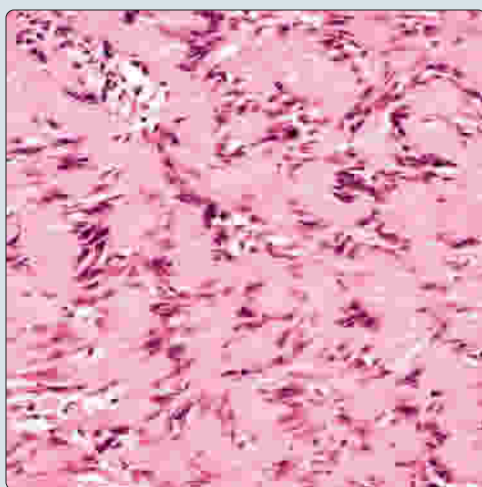


Palisading and Interlacing Fascicles

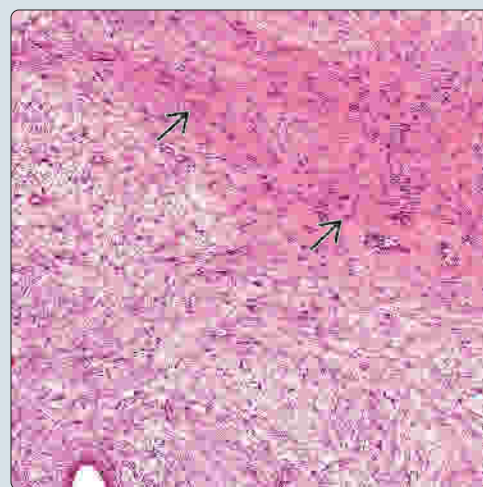


Palisaded Nuclei in Schwannoma

(Left) Hematoxylin and eosin shows spindled nuclei in a palisaded arrangement. There are abundant cellular processes between the nuclei (eosinophilic), creating a fibrillar material. (Right) The hypocellular appearance of spindled cells associated with myxoid and edematous Antoni B area is adjacent to an Antoni A cellular area. The nuclei are not atypical. Mitoses are absent.



Antoni A and B Areas in Schwannoma



TERMINOLOGY

Synonyms

- Peripheral nerve sheath tumor
- Neurilemmoma
- Acoustic neuroma, schwannoma, or neurinoma
- Vestibular neurilemmoma

Definitions

- Benign nerve sheath tumor arising within internal auditory canal (IAC) or intralabyrinthine

ETIOLOGY/PATHOGENESIS

Cell of Origin

- Schwann cell (myelin-forming) derived neoplasm
- Tumors arise along course of axons of vestibular portion of vestibulocochlear cranial nerve (CN VIII) from glial-Schwann sheath junction up to their terminations in auditory and vestibular end organs

Etiology

- Unknown for majority of cases
- Occupational exposure to extremely loud noise trauma, especially when sustained (20 years), may be risk factor in tumor development

CLINICAL ISSUES

Epidemiology

- Incidence
 - Accounts for 5-10% of all intracranial tumors
 - Most common neoplasm of temporal bone
 - Accounts for 80-90% of cerebellopontine angle (CPA) tumors
 - 95% of tumors are unilateral and sporadic
 - When bilateral or multicentric, high association with neurofibromatosis 2 (NF2)
- Age
 - Most common in 5th-6th decades
 - Tend to be younger (< 21 years) when associated with NF2

Site

- Cerebellopontine angle
 - If bilateral, consider NF2
- Internal auditory meatus

Presentation

- Hearing loss
 - Unilateral progressive hearing loss in 90% of patients
 - Sensorineural loss, **not** conductive
- Tinnitus (80% of patients): High-pitched ringing or steam-kettle-type hissing
- Headache
- Vertigo, often with nausea and vomiting
- Altered balance, with unsteady gait
- Facial pain, weakness, or loss of taste
 - Development of tumor compresses brainstem and so facial nerve (CN VII) is affected
- Symptoms are frequently present for years

Treatment

- Options, risks, complications
 - If tumor is small: Watchful waiting, monitoring by MR scanning, and using hearing aids (as needed)
 - Tumors tend to grow slowly
 - Especially advocated in older patients (> 70 years)
 - Nerve preservation more difficult in NF2 patients (tumors infiltrate nerves)
 - Attempt to maintain hearing and vestibular function
 - Meningitis is potential postoperative complication
- Surgical approaches
 - Translabyrinthine
 - Craniotomy with middle fossa or suboccipital approach to internal auditory canal
 - Anterior transpetrosal approach or subtemporal interdural approach (Dolenc)
 - Postoperative reconstruction for surgical defects
- Radiation
 - Stereotactic-guided gamma knife radiosurgery or fractionated stereotactic radiotherapy
 - May have failure rates up to 15%
 - Development of 2nd malignancy is a risk

Prognosis

- Excellent overall prognosis
 - When bilateral, multicentric or part of NF2, preservation of hearing and complete removal becomes more difficult
- Low recurrence potential
 - If radiated, tumors may be more difficult to remove
- Rare reports of malignant peripheral nerve sheath development

IMAGING

General Features

- Cerebellopontine angle mass most common or posterior fossa intracanalicular mass
- Funnel-shaped widening of internal auditory canal or small indentation of bone
- Mushroom shape: Stalk within canal; flange within CPA
- Virtual endoscopy shows promise as reconstructed views can create images used in surgical planning

MR Findings

- Hyperintense mass on T2WI (with gadolinium)

CT Findings

- Isodense to cerebellum and IAC widening
- Calcifications and blood may be seen

MACROSCOPIC

General Features

- Eccentric, globular mass
- Frequently attached to vestibular division of 8th (vestibulocochlear) cranial nerve
 - If associated with cochlear division, nerve is stretched rather than attached
- Smooth, lobulated tumor surface
- Firm, yellowish-tan, solid to cystic mass
- Intratumoral hemorrhage is common

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
S100	Positive	Nuclear & cytoplasmic	Strong and diffuse
SOX10	Positive	Nuclear	Strong and diffuse
Vimentin	Positive	Cytoplasmic	Strong but nonspecific
GFAP	Positive	Cytoplasmic	Occasionally positive
NSE	Positive	Cytoplasmic	Occasionally positive
Ki-67	Positive	Nuclear	Higher rates in NF2-associated tumors
CK-PAN	Negative		
EMA	Negative		
NFP	Negative		
Desmin	Negative		
Actin-sm	Negative		
Actin-HHF-35	Negative		
CD34	Equivocal	Cytoplasmic	Only stains isolated, slender cells in degenerated areas

Size

- Variable, usually < 2 cm
 - Tumors > 1.8 cm more likely to recur

MICROSCOPIC

Histologic Features

- Cellular (Antoni A) closely packed spindle cells
- Palisaded nuclei (Verocay body)
- Microcystic or loosely reticular Antoni B areas
- Cells are fusiform with fibrillary cytoplasm and buckled nuclei
- Mitotic figures are uncommon
- Medium-sized vessels with perivascular hyalinization
- Extensive degeneration results in only isolated tumor cells
- Necrosis is usually absent
- Lymphoid cuffing or peripheral infiltrate is absent in this location
- Extensive pleomorphism, necrosis and increased mitoses suggests malignancy
 - Ancient change can be seen but only in isolated cells

ANCILLARY TESTS

Immunohistochemistry

- Strong and diffuse S100 protein and SOX10 immunoreactivity

Genetic Testing

- Neurofibromatosis is autosomal dominant
 - *NF2* is suppressor gene on long arm of chromosome 22 (22q12)
 - 90% of mutations coded by merlin or schwannomin result in loss of protein function

Electron Microscopy

- Interdigitating slender cytoplasmic processes covered by continuous basal lamina
- Long spacing collagen with distinct periodicity (Luse body)

DIFFERENTIAL DIAGNOSIS

Meningioma

- Whorled appearance with occasional psammoma bodies
- Intracellular cytoplasmic inclusions
- EMA or focal keratin immunoreactivity

Neurofibroma

- Lacks Antoni A and B areas or perivascular hyalinization
- Very rare in this anatomic site
- NFP may be immunoreactive

Solitary Fibrous Tumor

- Cellular neoplasm, with spindle cells arranged in short fascicles associated with collagen
- CD34 and bcl-2 immunoreactive

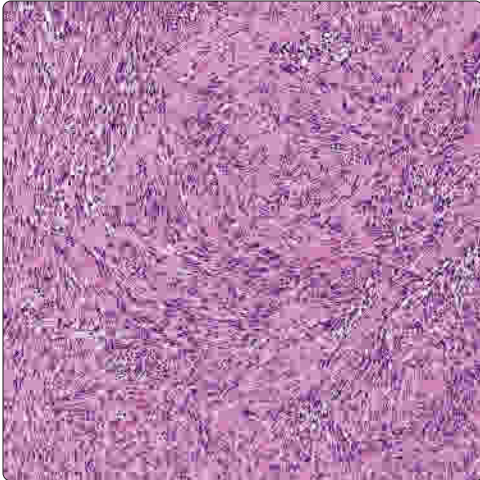
Malignant Peripheral Nerve Sheath Tumor

- Extensive pleomorphism, necrosis and increased mitoses suggests malignancy

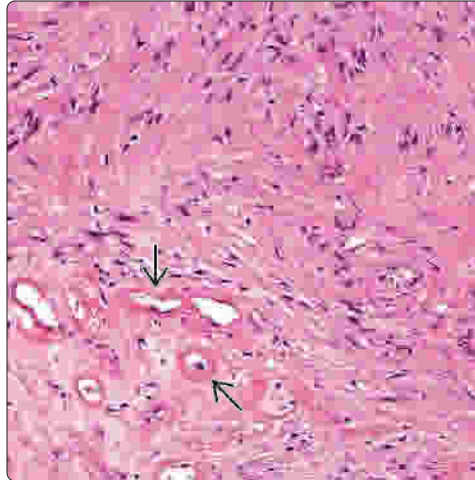
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Interlacing Fascicles in Schwannoma

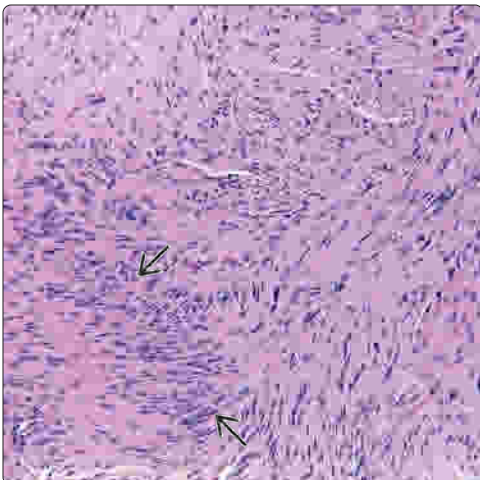


Peritheliomatous Hyalinization

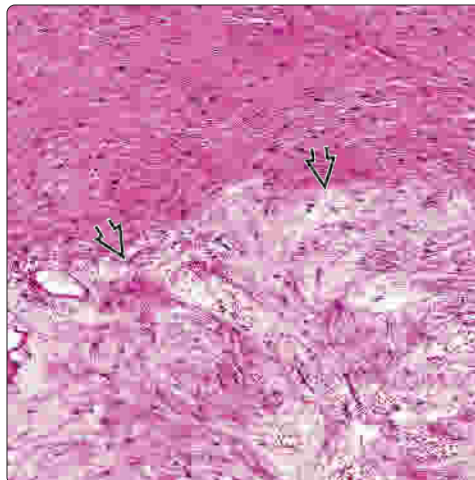




(Left) There are sweeping and interlacing fascicles of spindled cells in this IAC schwannoma. Nuclear palisading is noted. **(Right)** Perivascular hyalinization  is noted around a number of vessels in this schwannoma. There is hypocellularity with spindled cells arranged in interconnecting fascicles.

Palisaded Nuclei in Schwannoma

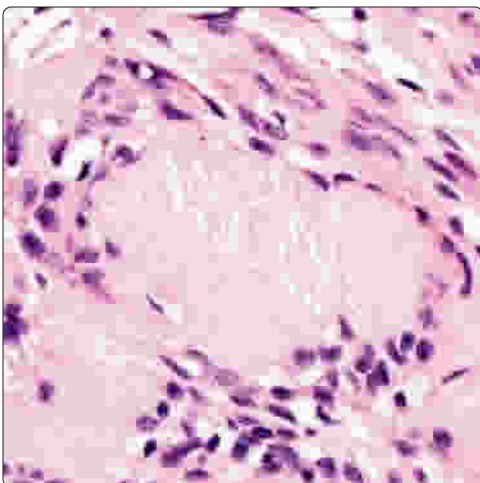


Antoni B Area With Degeneration

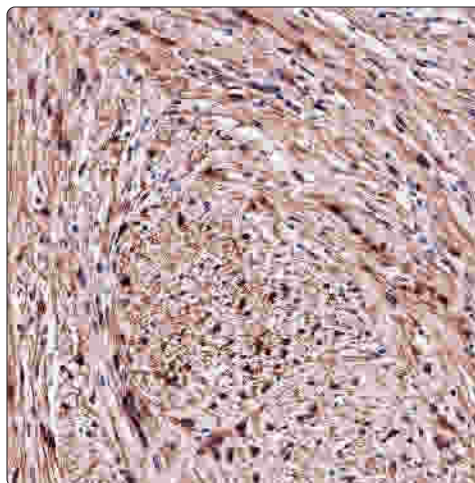


(Left) Short fascicles of spindled cells with well-developed palisaded nuclei  are seen. There is slight variability in cellularity, but all of the tissue in this field is from an Antoni A area. **(Right)** Hematoxylin & eosin shows areas of degeneration and edema (Antoni B ) within a schwannoma. A juxtaposition of hypo- and hypercellular areas is quite common in schwannoma.

Verocay Body in Schwannoma



S100 Protein Positive Neoplastic Cells



(Left) Hematoxylin and eosin shows a well-formed Verocay body, creating palisaded nuclei around an eosinophilic acellular center. **(Right)** The spindled cells of schwannoma are highlighted with nuclear and cytoplasmic reactivity with S100 protein. The staining highlights the growth pattern of the tumor. This reaction is neither specific nor sensitive for schwannoma but does help separate it from other mesenchymal spindle cell lesions in the ear/temporal bone.

Meningioma

KEY FACTS

TERMINOLOGY

- Benign neoplasm of meningotheial cells within ear and temporal bone

CLINICAL ISSUES

- Mean age: 50 years; range: 10-90 years
- Female > male (2:1)
- Site: Internal auditory meatus, middle ear jugular foramen, eustachian tube roof
- Hearing loss, tinnitus, otitis, pain
- Wide excision with clear margins is treatment of choice
- Recurrences in ~ 20% of patients

IMAGING

- Must **exclude** direct CNS extension

MACROSCOPIC

- Infiltrative lesion, usually < 1.5 cm

MICROSCOPIC

- Meningothelial and whorled architecture
- Lobules and nests of tumor cells, sometimes with concretions
- Epithelioid cells with syncytial architecture
- Intranuclear cytoplasmic inclusions
- Psammoma bodies or pre-psammoma bodies are frequent

ANCILLARY TESTS

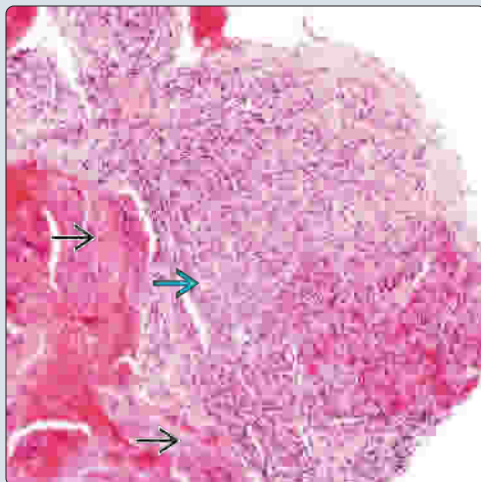
- **Positive:** EMA, pan-cytokeratin and CK7 (pre-psammomatous pattern), CAM5.2
- **Negative:** Chromogranin, synaptophysin, GFAP

TOP DIFFERENTIAL DIAGNOSES

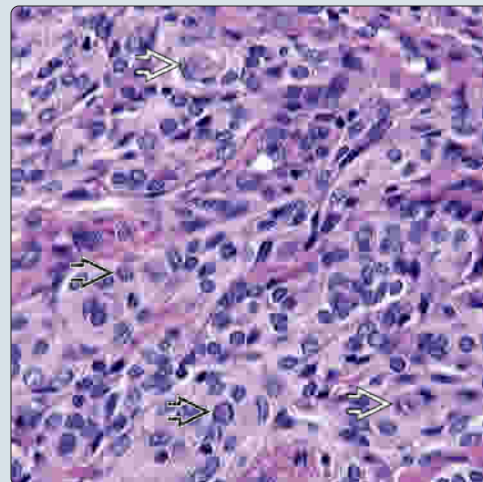
- Schwannoma
- Paraganglioma
- Neuroendocrine adenoma of middle ear
- Meningocele
- Ceruminous adenoma

Polypoid Mass in Middle Ear

(Left) Hematoxylin and eosin shows a polypoid mass adjacent to bone. Note the vague whorled pattern. There is fibrous connective tissue at the edge, but it is not forming a capsule. Concretions are present. (Right) Hematoxylin and eosin shows a meningothelial and whorled pattern with syncytial cells. Nuclei are round to oval and bland, containing a number of intranuclear cytoplasmic inclusions.

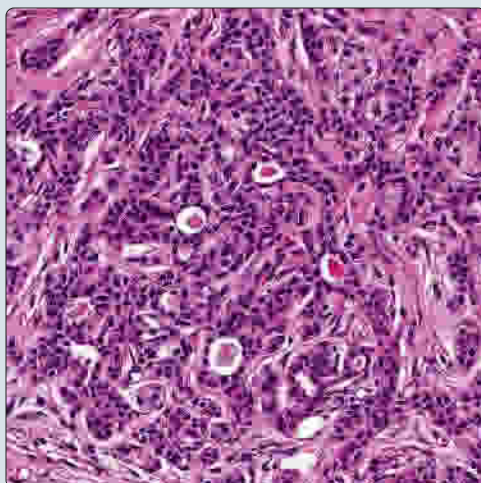


Meningothelial Pattern With Intranuclear Inclusions

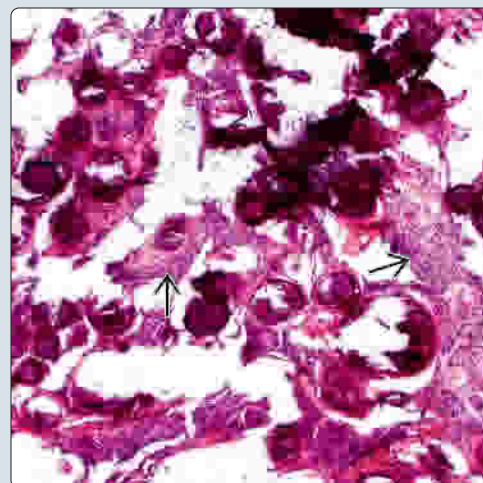


Corded Growth With Concretions

(Left) This nested pattern with concretions can easily be misdiagnosed as a neuroendocrine adenoma of middle ear. However, in other areas, a more meningothelial pattern of growth was seen with appropriate immunohistochemistry reactions. (Right) Innumerable psammoma bodies are noted in this psammomatous meningioma. The meningothelial proliferation is partially obscured by the calcifications.



Psammomatous Meningioma



TERMINOLOGY

Definitions

- Benign neoplasm of meningotheial cells within ear and temporal bone

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~ 10% of ear and temporal bone tumors
- Age
 - Mean: 50 years; range: 10-90 years
 - Women tend to be older than men at presentation
- Sex
 - Female > male (2:1)

Site

- Internal auditory meatus, middle ear jugular foramen, eustachian tube roof

Presentation

- Hearing loss, tinnitus
- Otitis, pain
- Headaches, dizziness, vertigo

Treatment

- Involvement of skull base makes treatment more complex
- Wide excision with clear margins is treatment of choice
- Radiation used for patients who are poor surgical candidates

Prognosis

- Good: 80% 5-year survival
- Recurrences in ~ 20% of patients (but may be residual or persistent disease)
- Patients die from complications of CNS involvement (mastoiditis and meningitis), including sepsis

IMAGING

General Features

- Must **exclude** direct CNS extension
- En plaque lesions must be actively sought and excluded
- Temporal air cell opacification
- Bone erosion, sclerosis, or hyperostosis

MACROSCOPIC

General Features

- Infiltrative lesion into bone
- Skin &/or mucosa is usually intact
- Granular, gritty material with calcifications

Size

- Mean: < 1.5 cm

MICROSCOPIC

Histologic Features

- Virtually all tumors are low grade (WHO Grade I)
- Tumor cell infiltration into bone, skin/mucosa, or soft tissues

- Infiltration does not alter patient outcome or management

- Meningothelial and whorled architecture
- Lobules and nests of tumor cells, sometimes with concretions
- Epithelioid cells with syncytial architecture
- Bland, round to oval nuclei with delicate nuclear chromatin
- Intranuclear cytoplasmic inclusions
- Psammoma bodies or pre-psammoma bodies are frequent

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** EMA, pancytokeratin and CK7 (patchy, ring-shaped staining surrounding pre-psammomatous areas), CAM5.2
- **Negative:** Chromogranin, synaptophysin, GFAP

DIFFERENTIAL DIAGNOSIS

Schwannoma

- Alternating cellular and hypocellular regions, often with cystic and degenerative changes, with perivascular hyalinization
- Usually very strong S100 protein immunoreactivity

Paraganglioma

- Zellballen, organoid, or nested architecture, with prominent but isolated pleomorphism
- Chromogranin/synaptophysin **positive**, with sustentacular S100 protein reaction

Neuroendocrine Adenoma of Middle Ear

- Middle ear tumor with organoid growth, salt and pepper nuclear chromatin, and neuroendocrine immunohistochemistry

Meningocele

- Acquired (postsurgical, infectious, or traumatic) or congenital
- Usually cystic with direct extension from CNS

Ceruminous Adenoma

- External auditory canal, biphasic tumor with apocrine snouting, and ceroid pigment
- Biphasic epithelial and myoepithelial/basal immunophenotype

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Langerhans Cell Histiocytosis

KEY FACTS

TERMINOLOGY

- Clonal proliferation of Langerhans cells
 - Occurs as isolated lesion or part of systemic (multifocal) proliferation
- Langerhans cell histiocytosis used to replace previous nomenclature of group of diseases termed histiocytosis X that included eosinophilic granuloma, Letterer-Siwe syndrome, and Hand-Schüller-Christian disease

CLINICAL ISSUES

- Most common in 2nd-3rd decades
- Different therapeutic approaches can be considered depending on affected organ, including surgery, radiotherapy, and chemotherapy
- Surgical excision (curettage) and low-dose radiotherapy for isolated temporal bone disease
- Chemotherapy used for multifocal and systemic disease
- Recurrence may be part of systemic or multifocal process and generally occurs within 6 months of diagnosis

- Prognosis for isolated disease considered very good

IMAGING

- Single or multiple, circumscribed, osteolytic lesions



MICROSCOPIC

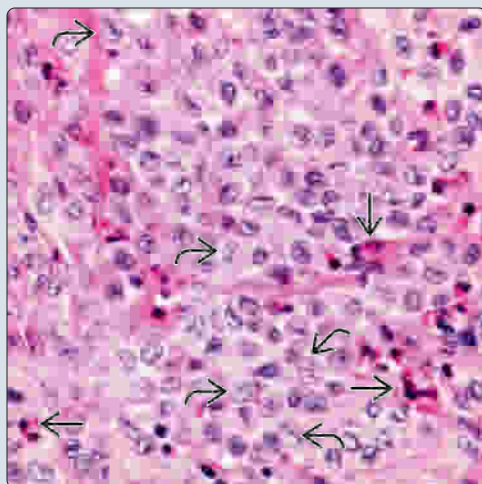
- Langerhans cells
 - Enlarged nuclei with vesicular chromatin, inconspicuous to small, centrally located, basophilic nucleoli, eosinophilic cytoplasm
 - Characteristic reniform nuclei showing nuclear membrane lobations or indentations
 - Accompanied by inflammatory cell infiltrate
 - Primarily eosinophils but may include lymphocytes, plasma cells, neutrophils

ANCILLARY TESTS

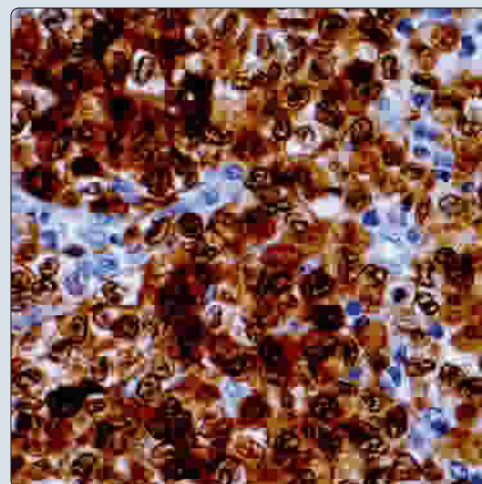
- **Positive** for S100 protein, CD1a, and Langerin
- Detection of *BRAFV600E* mutation
 - May provide opportunities for devising targeted therapy

Langerhans Cells


(Left) Intraosseous (not shown) sheet-like proliferation of Langerhans cells is characterized by the presence of cells with vesicular nuclei, lobation of the nuclear membrane , and a variably admixed inflammatory cell infiltrate, including eosinophils . (Right) Langerhans cells are diffusely immunoreactive for S100 protein, including nuclear and cytoplasmic reactivity. The background inflammatory cells lack S100 protein staining.

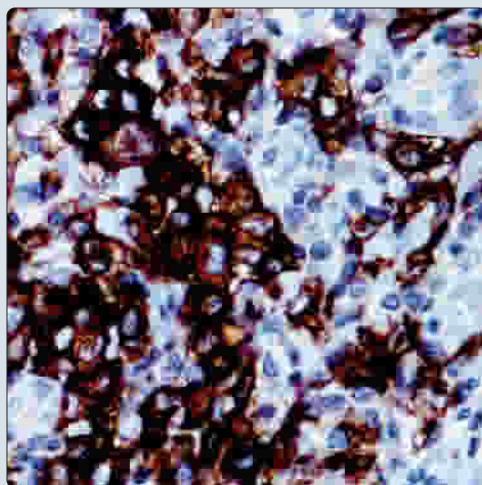


Langerhans Cells, S100 Protein Positive

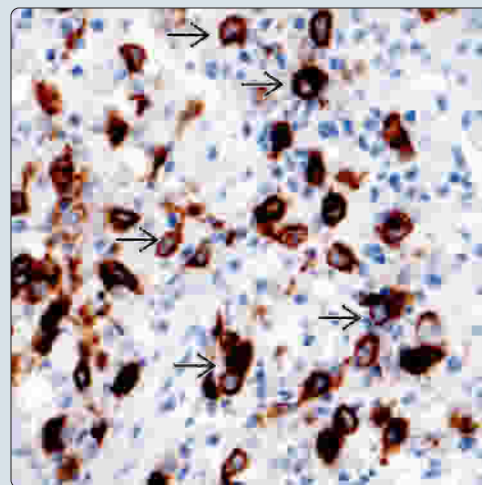


Langerhans Cells, CD1a Positive

(Left) Langerhans cells are diffusely and strongly immunoreactive for CD1a (cytoplasmic). (Right) Langerhans cells show immunoreactivity for Langerin . Based on the light microscopic features coupled with the immunoreactivity for S100 protein, CD1a, and Langerin, a diagnosis of Langerhans cell histiocytosis is confirmed and allows differentiation from other lesions, such as Rosai-Dorfman disease.



Langerhans Cells, Langerin Positive



TERMINOLOGY

Abbreviations

- Langerhans cell histiocytosis (LCH)

Synonyms

- Langerhans cell (eosinophilic) granulomatosis
- Designation of LCH is used to replace previous nomenclature of group of diseases termed histiocytosis X that included eosinophilic granuloma, Letterer-Siwe syndrome, and Hand-Schüller-Christian disease

Definitions

- Clonal proliferation of Langerhans cells (component of dendritic cell system) occurring as isolated lesion or part of systemic (multifocal) proliferation

CLINICAL ISSUES

Epidemiology

- Age
 - Most common in 2nd-3rd decades
- Sex
 - Male > female

Presentation

- Lesions are most often osseous based
 - Most frequent osseous sites involved occur in skull (including middle ear and temporal bone)
- In patients with middle ear and temporal bone involvement
 - Aural discharge, swelling of temporal bone area, otitis media, bone pain/otalgia, hearing loss, vertigo

Treatment

- Different therapeutic approaches can be considered depending on affected organ, including surgery, radiotherapy, and chemotherapy
 - Surgical excision (curettage) and low-dose radiotherapy for isolated temporal bone disease
 - Chemotherapy used for multifocal and systemic disease

Prognosis

- Recurrence may be part of systemic or multifocal process and generally occurs within 6 months of diagnosis
- Prognosis for isolated disease considered very good
 - Failure of new bone lesion to occur within 1 year of diagnosis considered cure
- Adverse prognostic findings
 - Younger age at onset
 - More extensive involvement (multiple sites, including bone and viscera)

IMAGING

General Features

- Single or multiple, sharply circumscribed, osteolytic lesions

MICROSCOPIC

Histologic Features

- Langerhans cells
 - Enlarged nuclei with vesicular chromatin, inconspicuous to small, centrally located, basophilic nucleoli, eosinophilic cytoplasm

- Characteristic reniform nuclei showing nuclear membrane lobations or indentations
- Nuclear pleomorphism, mitotic figures are uncommon
- Foamy histiocytes and multinucleated giant cells may also be present
 - May show phagocytosis of mononuclear cells
- Accompanied by inflammatory cell infiltrate
 - Primarily eosinophils but may include lymphocytes, plasma cells, neutrophils

ANCILLARY TESTS

Immunohistochemistry

- **Positive** for S100 protein, CD1a, and Langerin
 - CD163 may be identified

Genetic Testing

- Detection of *BRAF*V600E mutation
 - May provide opportunities for devising targeted therapy

Electron Microscopy

- Elongated cytoplasmic granules (Langerhans or Birbeck granules) may be seen

DIFFERENTIAL DIAGNOSIS

Extranodal Sinus Histiocytosis With Massive Lymphadenopathy (Rosai-Dorfman)

- **Positive** for S100 protein and CD68
- **Negative** for CD1a and Langerin

Non-Hodgkin Malignant Lymphoma

- Differentiation from LCH by light microscopy usually not problematic
 - Lymphoma cells show lineage specificity (B or T cell), lack S100 protein, CD1a, and Langerin

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Atypical Fibroxanthoma

KEY FACTS

TERMINOLOGY

- Atypical fibroxanthoma (AFX)
- Superficial malignant fibrous histiocytoma (MFH)/pleomorphic sarcoma
- Dermal-based, low-grade mesenchymal neoplasm showing no specific lineage of differentiation

CLINICAL ISSUES

- Mass lesion, may be ulcerated or bleeding
- Often rapidly growing tumor in head and neck region of elderly adult with heavy UV/sun exposure history
- Rate of local recurrence is low (< 10% reported)

MICROSCOPIC

- Highly atypical and pleomorphic dermal-based proliferation of spindled to epithelioid-appearing cells
- Scattered large, bizarre-appearing multinucleated cells often seen

- Variants include spindle cell, clear cell, granular, chondroid, and osteoid
- Numerous mitoses, including highly atypical forms, easily found





ANCILLARY TESTS

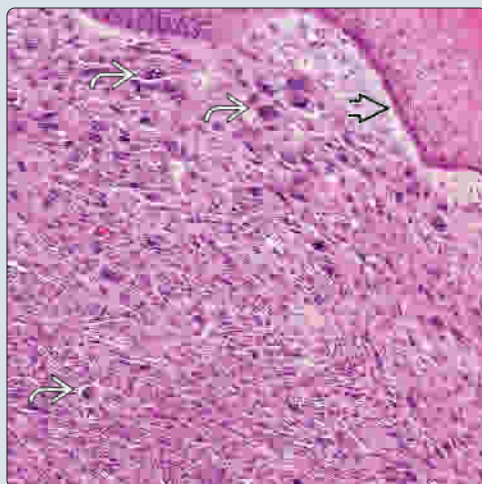
- Immunohistochemistry is key in confirming diagnosis
 - Essential to exclude other, more specific diagnoses
- **Negative** for melanocytic markers, cytokeratins (CK5/6, 34βE12), p63, muscle (except for SMA), and vascular markers
- **Positive** for nonspecific markers including CD10, CD68, CD99, and vimentin

TOP DIFFERENTIAL DIAGNOSES

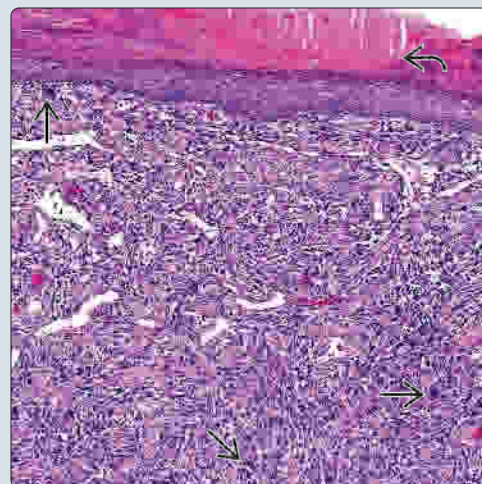
- Spindle cell/sarcomatoid squamous cell carcinoma
- Spindle cell, pleomorphic, and desmoplastic melanoma
- Pleomorphic dermal sarcoma
- Rarely, other sarcomas (leiomyosarcoma, angiosarcoma, dermatofibrosarcoma protuberans)

Superficial Dermal Portion of AFX






(Left) Histologic examination of the superficial portion of an AFX shows a proliferation of markedly atypical spindled and epithelioid-shaped cells, with numerous large multinucleated tumor cells  also seen. The tumor closely abuts but does not involve the overlying epidermis . (Right) Low magnification of AFX shows a cellular and sheet-like atypical dermal-based proliferation of spindle-shaped and pleomorphic  cells. The epidermis shows dense overlying serum crusting .

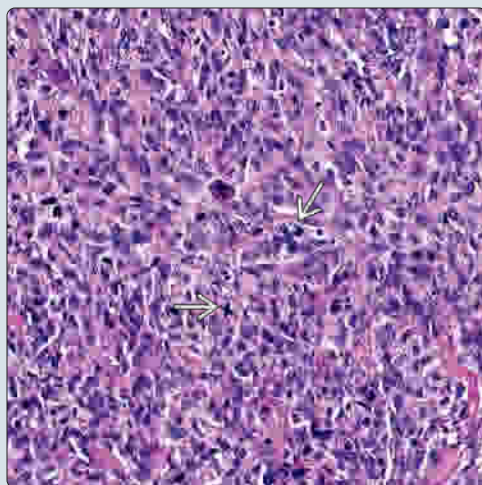


Highly Atypical Storiform Pleomorphic Dermal Population

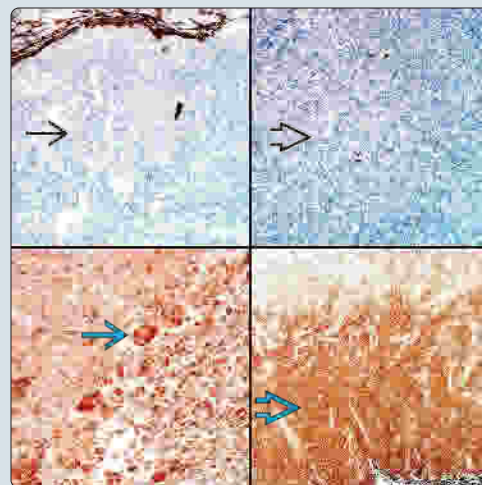


Atypical Mitoses and Pleomorphic Tumor Cells

(Left) Higher magnification of an AFX shows a proliferation of markedly atypical and pleomorphic-appearing enlarged, epithelioid to spindle-shaped cells, with several atypical mitoses . (Right) The neoplastic cells of an AFX are negative with HMWCK  (such as CK5/6, 34βE12), and S100 protein . However, the neoplastic cells are positive with both CD68  and CD10 , nonspecific markers in this setting. The diagnosis is usually made based on negative epithelial, melanoma, and muscle markers.



Composite IHC Results



TERMINOLOGY

Abbreviations

- Atypical fibroxanthoma (AFX)

Definitions

- Dermal-based, low-grade mesenchymal neoplasm showing no specific lineage of differentiation

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Likely related to UV exposure, as most cases occur in elderly patients in areas of sun-damaged skin

CLINICAL ISSUES

Epidemiology

- Age
 - Typically occurs in elderly patients
 - Rare cases in children with xeroderma pigmentosum or Li-Fraumeni syndrome
- Sex
 - Slight male predominance

Site

- Head and neck is most commonly affected area (scalp specifically)
- Strong association with marked ultraviolet/sun exposure

Presentation

- Skin nodule, asymptomatic in most cases, but may be rapidly growing lesion
 - Often shows overlying ulceration or bleeding/crusting
- Regional lymph node metastases may be found in small number of cases

Treatment

- Complete, wide surgical excision (Mohs surgery effective)
- Unresectable or metastatic cases may be treated with chemoradiation

Prognosis

- Very good, with < 10% reported rate of local recurrence
- Vast majority of cases do not metastasize

MACROSCOPIC

General Features

- Large, nodular, unencapsulated, dermal-based tumor

Size

- < 2 cm in greatest dimension in most cases

MICROSCOPIC

Histologic Features

- Nodular, dermal-based proliferation of markedly enlarged, atypical, pleomorphic-appearing spindled and epithelioid-shaped cells
 - Atypical, hyperchromatic-staining nuclei, irregular nuclear borders and prominent nucleoli
 - Cytoplasm of tumor cells is abundant, eosinophilic, and sometimes foamy/vacuolated-appearing

- Variants include spindle cell, clear cell, granular, chondroid, and osteoid
- Scattered large, bizarre-appearing multinucleated giant cells typically present
- Numerous mitoses, including highly atypical forms, easily identified
- No evidence of associated/overlying carcinoma or melanoma in situ
 - Often separated from epidermis by thin Grenz zone

ANCILLARY TESTS

Immunohistochemistry

- A diagnosis of exclusion, gained with appropriate IHC, excluding other specific diagnoses
- **Negative:** S100 protein, HMB45, SOX10, Melan-A, cytokeratins (especially HMWCKs: CK5/6, 34βE12), p63, p40, muscle (except for SMA, which is typically focal/weak), CD34, CD31
- **Positive:** CD10, CD68, vimentin

DIFFERENTIAL DIAGNOSIS

Spindle Cell/Sarcomatoid Squamous Cell Carcinoma

- Surface origin, with markedly pleomorphic population
- **Positive:** CK5/6, 34βE12, p63, p40; **variable:** pancytokeratin, AE1/AE3, EMA, CAM5.2

Pleomorphic, Spindle Cell, and Desmoplastic Melanoma

- Overlying junctional component/melanoma in situ is present in majority of cases (> 70%)
- **Positive:** S100 and SOX10; ± Melan-A, HMB-45, tyrosinase, and MITF

Pleomorphic Dermal Sarcoma

- Head and neck of older/elderly men, involving deep subcutaneous/fascial/muscular tissues with necrosis &/or lymphovascular invasion
- Lacks identifiable lineage, size > 2 cm, poor circumscription, marked pleomorphism, high mitotic rate, coagulative necrosis

Leiomyosarcoma

- Proliferation of atypical spindle cells with elongated, blunt-ended, or cigar-shaped nuclei with perinuclear vacuoles
- **Positive:** MSA, SMA, desmin (most cases)

Other Sarcomas

- Angiosarcoma: Irregular, anastomosing vascular spaces; CD31(+), CD34(+)
- Malignant peripheral nerve sheath tumor: Usually deep-seated lesions; **positive:** SOX10, S100 protein
- Fibrosarcoma (FS): Usually arises in dermatofibrosarcoma protuberans (DFSP) in dermis or superficial subcutis
 - Prominent herringbone pattern in FS areas, storiforming in DFSP areas
 - DFSP shows strong CD34(+), usually (-) in FS areas

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Squamous Cell Carcinoma

KEY FACTS

TERMINOLOGY

- Squamous cell carcinoma (SCC)
 - Malignant epithelial tumor of squamous keratinocytes

ETIOLOGY/PATHOGENESIS

- Most cases are related to UV radiation
- Previous radiation therapy implicated in some cases, usually associated with more aggressive SCC

CLINICAL ISSUES

- Often arises in sun-damaged skin of elderly patients
 - Vast majority of cases associated with preexisting actinic keratosis (AK)
- May be ulcerated or bleeding
- Complete surgical excision is optimal and definitive therapy
- Prognosis usually good in superficial and well-differentiated cases
- Worse prognosis with poorly differentiated, deeply invasive, or aggressive subtypes

MICROSCOPIC



- Proliferation of invasive atypical keratinocytes, often with areas of keratinization (keratin pearls) and squamous eddies
- Cells are present in nests, sheets, cords and single cells
- Cytologically, cells show abundant eosinophilic cytoplasm, and large nucleus with vesicular chromatin and prominent nucleoli
- Degree of differentiation is variable, ranging from well to poorly differentiated
- Multiple variants of differing malignant potential described

TOP DIFFERENTIAL DIAGNOSES

- Basal cell carcinoma (BCC)
- Atypical fibroxanthoma (AFX)
- Poorly differentiated carcinoma (including metastatic)
- Pseudoepitheliomatous hyperplasia (PEH)
- Keratoacanthoma (KA)

Invasive, Well-Differentiated Squamous Cell Carcinoma at Cartilage

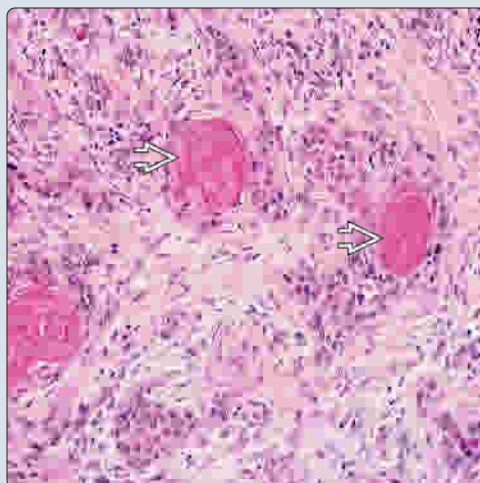




(Left) Invasive, well-differentiated keratinizing squamous cell carcinoma (SCC) of the ear invading up to  (but not into) the auricular cartilage. It is not uncommon to see deep invasion in this site. **(Right)** Invasive, well-differentiated SCC is seen arising in association with an actinic keratosis . There is an inflammatory infiltrate associated with the islands of tumor.

Invasive, Well-Differentiated Squamous Cell Carcinoma



Moderately Differentiated Invasive Squamous Cell Carcinoma



(Left) Moderately differentiated invasive SCC shows prominent keratin pearls  and a sclerotic stroma with scattered inflammatory cells. Cytoplasmic opacification is noted also. **(Right)** This high-power view shows tangentially sectioned SCC in situ with smooth borders  and lack of an infiltrative growth pattern. There is an overlying associated verruca vulgaris, an uncommon finding. There is an associated inflammatory cell infiltrate at the base of the lesion.

Squamous Cell Carcinoma In Situ Arising in Verruca



TERMINOLOGY

Abbreviations

- Squamous cell carcinoma (SCC)

Synonyms

- Sarcomatoid carcinoma (spindle cell carcinoma/carcinosarcoma/metaplastic carcinoma)
- Acantholytic (adenoid/pseudoglandular) SCC
- Verrucous squamous cell carcinoma (well-differentiated variant)
- Keratoacanthoma (KA) (very well-differentiated variant, regresses spontaneously)

Definitions

- Malignant tumor of squamous keratinocytes

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Most cases are related to UV radiation
- Some cases are likely related to chronic inflammation (i.e., SCC arising in burns, lupus, lichen planus)
- Previous radiation therapy: Usually associated with more aggressive SCC
- Chronic wounds and burn scars also can be associated with high-risk SCC
- HPV is associated with some cases
 - Especially verrucous carcinoma (low grade) and SCC in immunosuppressed patients (high grade)

CLINICAL ISSUES

Epidemiology

- Age
 - Usually in the elderly, especially solar-related lesions
 - Wide age range
 - Rare cases in children (should prompt genetic studies)
- Sex
 - Ear: More common in male patients

Presentation

- Slow-growing papular, nodular, or plaque lesion
- Often arises in sun-damaged skin
 - Vast majority of cases associated with preexisting actinic keratosis (AK)
- May be ulcerated or bleeding
- Ear canal and middle ear tumors may present with pain, hearing loss, and discharge

Treatment

- Surgical approaches
 - Complete surgical excision is optimal and definitive therapy
 - Mohs surgery has been shown to be highly effective for most tumors
- Drugs
 - If patients are not surgical candidates, topical chemotherapeutics or immunomodulators may be used
- Radiation
 - May be used for very advanced cases where surgical therapy is not curative

Prognosis

- Usually excellent in most cases
- Lip and ear tumors more aggressive, regardless of degree of differentiation
- Worse prognosis with poorly differentiated, deeply invasive, or rare aggressive subtypes

MACROSCOPIC

Size

- Remarkably variable; few mm to several cm

MICROSCOPIC

Histologic Features

- Proliferation of invasive atypical keratinocytes
 - Cells are present in nests, sheets, and infiltrative cords or single cells
 - Often show areas of keratinization (keratin pearls) and squamous eddies
 - Attachments to overlying epidermis in most cases (unless ulcerated)
 - Associated AK is very common; less likely, may be associated with SCC in situ (Bowen disease)
 - Cytologically, cells show abundant eosinophilic cytoplasm and large nucleus with vesicular chromatin and prominent nucleoli
 - Intercellular bridges (desmosomes) easily identified on high-power examination
 - Presence of dyskeratotic cells (apoptotic keratinocytes) within the proliferation is reliable sign of squamous differentiation
 - If no definite squamous differentiation is present, immunohistochemistry should be employed to confirm diagnosis
- Degree of differentiation is variable, ranging from well to poorly differentiated
 - Amount of keratinization typically decreases and cytologic atypia increases with higher grades
 - Mitotic figures are usually numerous, and atypical forms are found especially in moderately to poorly differentiated cases
- Multiple variants of differing malignant potential described
 - Low-risk variants
 - Well-differentiated SCC arising in AK, keratoacanthoma, verrucous squamous cell carcinoma, and trichilemmal (variant of clear cell) carcinoma
 - Intermediate-risk variants
 - Acantholytic (adenoid/pseudoglandular) and lymphoepithelioma-like carcinoma of the skin
 - High-risk variants
 - Spindle cell/sarcomatoid, basaloid, adenosquamous, and desmoplastic
 - Also, radiation, burn scar, and immunosuppression-related SCCs
 - Rare variants of uncertain malignant potential include clear cell SCC, signet ring cell SCC, follicular SCC, papillary SCC, pigmented SCC, and SCC arising from adnexal ducts or cysts

ANCILLARY TESTS

Immunohistochemistry

- Not necessary in well- or moderately differentiated cases but may be needed in poorly differentiated and spindle cell cases
- Cytokeratins are most important markers, especially high molecular weight cytokeratins (HMWCKs)
 - HMWCKs are most sensitive markers for poorly differentiated and spindle cell/sarcomatoid SCC
 - CK5/6 and K903 most useful
 - Pankeratin can be lost in poorly differentiated and spindle cell cases
 - p63 is also a very sensitive marker and can be used in addition to HMWCK to confirm diagnosis
 - p40 (squamous-specific isoform of p63) is a very sensitive marker of squamous differentiation
- Vimentin may be **positive** in spindle cell/sarcomatoid cases
- **Negative** staining for other markers, including
 - **Melanoma**: S100 protein, SOX10, Melan-A, and HMB-45
 - **AFX**: CD10, CD68, and CD99
 - **Leiomyosarcoma**: Actin-sm and desmin
 - **BCC and sebaceous carcinoma**: BER-EP4, androgen receptor (AR), and D2-40

DIFFERENTIAL DIAGNOSIS

Basal Cell Carcinoma

- Cells are typically smaller, more hyperchromatic, and show peripheral palisading, mucinous stroma, and retraction artifact
- Cytokeratins do not distinguish basal cell carcinoma (BCC) from SCC, but BER-EP4 and AR are almost always **positive** in BCC, while **negative** in SCC

Atypical Fibroxanthoma

- Usually large, nodular lesion in heavily sun-damaged skin
- Immunohistochemistry is essential in excluding poorly differentiated SCC
 - SCC is typically **positive** for HMWCKs, p63, p40
 - Atypical fibroxanthoma is **negative** for these markers and often **positive** for CD10, CD68, and CD99

Poorly Differentiated Carcinoma (Including Metastatic)

- Clinical history and imaging studies are paramount, as immunohistochemistry may not be able to distinguish some cases from primary SCC
- Adenocarcinomas may show varying degree of ductal/glandular differentiation
 - If present, ductal spaces can be highlighted with markers such as EMA and CEA

Pseudoepitheliomatous Hyperplasia

- Can mimic SCC, especially SCC in situ, but does not show infiltrative features or high-grade cytologic atypia
- Mitotic figures can be numerous but should be in basilar keratinocytes and non-atypical

Keratoacanthoma

- Essentially a well-differentiated variant of SCC that spontaneously regresses in most cases

- Typically composed of large, crateriform (cup-like) lesion filled with abundant keratin debris
- Cells are enlarged, with abundant glassy-appearing/hyalinized cytoplasm
- Most cases regress, but giant keratoacanthoma can be aggressive; some may metastasize in immunosuppressed patients

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Degree of differentiation
- Depth of invasion
 - Deeply invasive tumors have much higher rates of recurrence and metastasis
- Perineural invasion
 - Tumors with perineural invasion have high rates of local recurrence and increased risk of metastasis
- Lymphovascular invasion

Pathologic Interpretation Pearls

- Adjacent or overlying AK often present in external ear cases
- Invasive proliferation of epithelioid cells, with areas of keratinization (keratin pearls) and squamous eddies
 - Intercellular bridges (desmosomes) and dyskeratotic cells confirm squamous differentiation in poorly differentiated cases

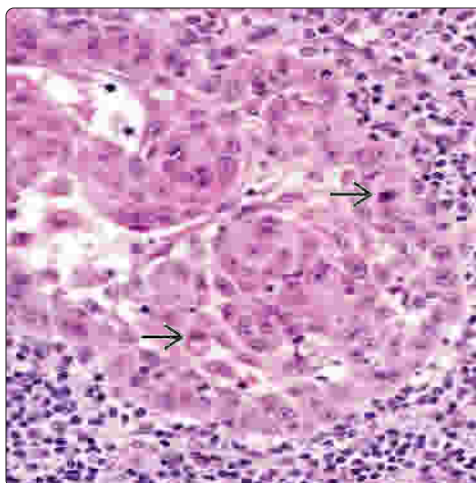
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Clinical Photograph of Ear Squamous Cell Carcinoma

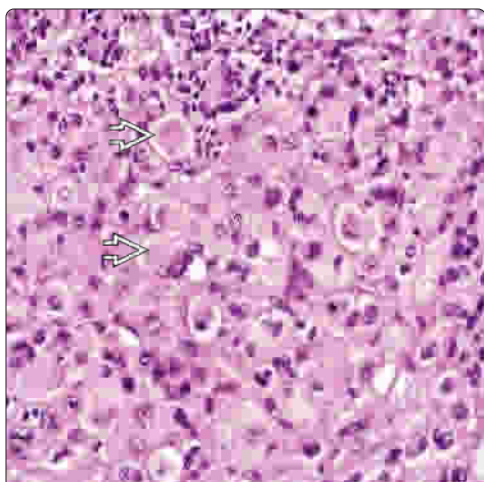


High Magnification of Acantholytic Squamous Cell Carcinoma

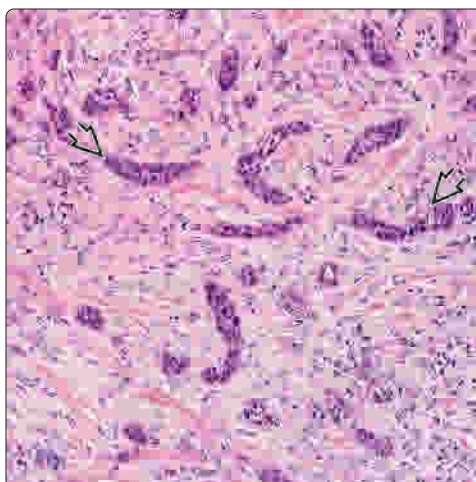


(Left) There is a large exophytic mass on the helix of the ear showing crusting and ulceration. On biopsy, this proved to be a squamous cell carcinoma. (Right) High-power view of an acantholytic SCC shows large epithelioid cells with dense eosinophilic cytoplasm and scattered dyskeratotic (apoptotic) cells. There is an associated heavy inflammatory cell infiltrate.

Poorly Differentiated Squamous Cell Carcinoma

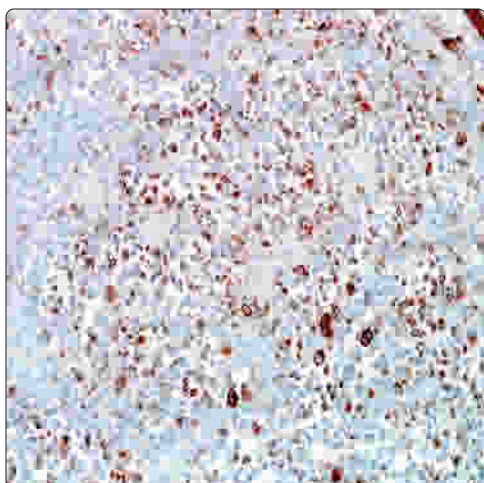


Poorly Differentiated Squamous Cell Carcinoma With Desmoplasia

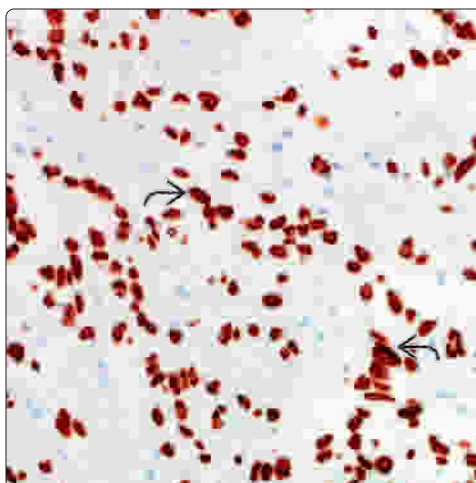


(Left) High-grade invasive SCC shows a sheet-like proliferation of atypical and pleomorphic epithelioid and multinucleated cells with hyperchromatic nuclei, prominent nucleoli, and abundant glassy-appearing eosinophilic cytoplasm. Keratinization is not seen. (Right) This is an example of a poorly differentiated infiltrating squamous cell carcinoma forming cords (mimicking ductal structures). There is an associated dense desmoplastic stroma. These findings may mimic those of skin adnexal tumors.

CK5/6 in Poorly Differentiated Squamous Cell Carcinoma



p63 in Poorly Differentiated Squamous Cell Carcinoma



(Left) High-power image of CK5/6 (HMWCK) immunohistochemistry showing moderate to strong cytoplasmic staining of many of the neoplastic cells. (Right) High-power view of p63 immunohistochemistry shows strong and diffuse nuclear staining of large, irregularly shaped nuclei in a poorly differentiated infiltrating SCC.

Basal Cell Carcinoma

KEY FACTS

TERMINOLOGY

- Basal cell carcinoma (BCC): Low-grade malignancy of basal keratinocytes

ETIOLOGY/PATHOGENESIS

- Related to sun exposure, radiation, immunosuppression
- Rare cases are syndrome associated: Nevoid basal cell carcinoma (Gorlin) syndrome (*PTCH1*), xeroderma pigmentosum (*XPA*, *TP53*)

CLINICAL ISSUES

- Very common: Most common cancer in humans
- Most common in head and neck region (up to 80% of cases)
- Typically older adults; few cases in young adults (consider inherited syndrome)
- Often present as pearly, translucent papule with telangiectasia
- Prognosis usually excellent, most cases cured by complete excision or electrodesiccation and curettage

- More aggressive subtypes, including infiltrative, micronodular, desmoplastic, and basosquamous, have higher rate of recurrence and low risk of metastasis

MICROSCOPIC

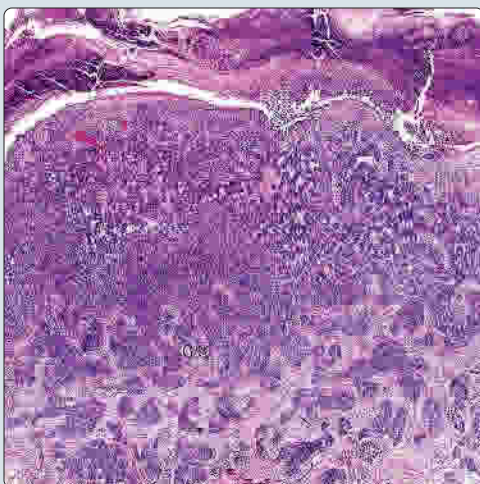
- Proliferation of nodules, nests, and cords of small basaloid cells with peripheral palisading of nuclei, stromal retraction artifact, and mucinous material
- Numerous mitotic and apoptotic figures typically present
- Cells show enlarged hyperchromatic nuclei with inconspicuous nucleoli and scant amounts of cytoplasm

TOP DIFFERENTIAL DIAGNOSES

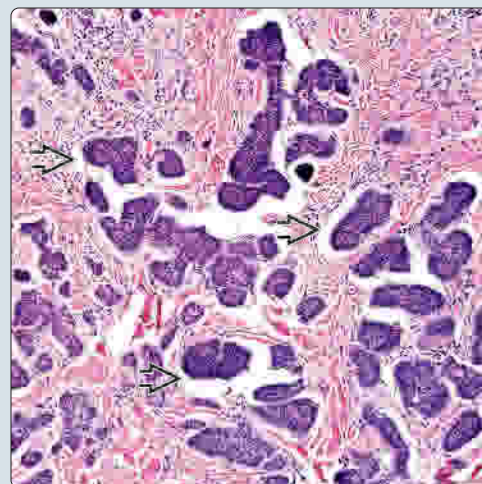
- Squamous cell carcinoma
- Actinic keratosis (on superficial shave biopsy)
- Merkel cell carcinoma
- Sebaceous carcinoma
- Follicular neoplasms (trichoepithelioma and trichoblastoma)

Basal Cell Carcinoma at Low Magnification

(Left) Low magnification shows a large nodular- and micronodular-type basal cell carcinoma (BCC) with diffuse overlying ulceration and dense serum crust containing degenerating neutrophils. Note tumor infiltration at the base. (Right) A micronodular-type BCC shows a proliferation of small, infiltrative nests of basaloid cells with prominent retraction artifact in a somewhat sclerotic-appearing stroma. The retraction is between the tumor cells and the stroma.

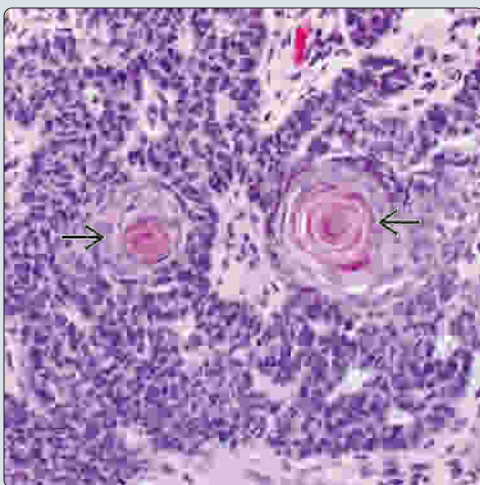


Micronodular Type BCC With Stromal Retraction

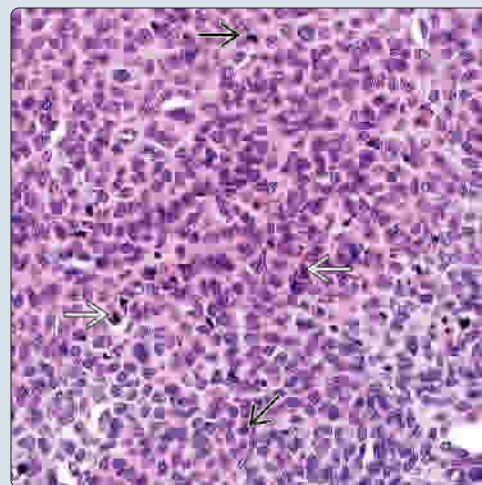


Focal Keratinization in BCC

(Left) This basal cell carcinoma shows focal keratinization. It is not uncommon to see squamous nests, eddies, or keratin pearls within a basal cell carcinoma. In superficial biopsies, separation from squamous cell carcinoma may be challenging. (Right) This nodular BCC shows a sheet-like proliferation of atypical basaloid cells with high N:C ratios and numerous apoptotic and mitotic figures. These latter findings can help in separation from tumors in the differential diagnosis.



Basaloid Cells With Numerous Mitoses



TERMINOLOGY

Abbreviations

- Basal cell carcinoma (BCC)

Definitions

- Low-grade malignancy of basaloid-appearing keratinocytes

ETIOLOGY/PATHOGENESIS

Multifactorial

- Related to sun exposure (vast majority of cases); radiation, immunosuppression, burn scars

Genetics

- Rare cases are syndrome associated: Nevroid basal cell carcinoma (Gorlin) syndrome (*PTCH1*), xeroderma pigmentosum (*XPA*, *TP53*)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very common: Most common cancer in humans
- Age
 - Typically older adults; few cases in young adults (consider inherited syndrome)
- Sex
 - Slight male predilection
- Ethnicity
 - Caucasian/light-skinned individuals

Presentation

- Most common in head and neck region (up to 80% of cases)
- Often present as pearly, translucent papule with telangiectasia; ulcerated with crusting

Treatment

- Complete excision or electrodesiccation and curettage
- Mohs micrographic surgery often used in facial cases

Prognosis

- Usually excellent, cured by local excision
- More aggressive subtypes, including micronodular, infiltrative, desmoplastic, and basosquamous, have higher rate of recurrence and increased risk of metastasis

MACROSCOPIC

Size

- Variable, small (few mm) to large (several cm)

MICROSCOPIC

Histologic Features

- Tumor is composed of nodules, nests, &/or infiltrative cords
 - Overlying ulceration and serum crusting often present
- Proliferation of small basaloid cells with peripheral palisading of nuclei
- Stromal retraction artifact between tumor cells and stroma
- Mucinous material may be present
- Numerous mitotic and apoptotic figures present
- Enlarged hyperchromatic nuclei with inconspicuous nucleoli and scant cytoplasm

- Focal areas of keratinization or sebaceous differentiation may be seen

Variants

- **Superficial-multicentric:** Superficial nests attached to epidermis separated by areas of uninvolved epidermis
- **Micronodular:** Predominantly dermal-based infiltrative proliferation of small nests
- **Desmoplastic/sclerosing/morpheaform:** Infiltrative strands and nests with dense sclerotic stroma
- **Basosquamous/metatypical:** Prominent areas of squamous differentiation with less peripheral palisading of nuclei present

ANCILLARY TESTS

Immunohistochemistry

- Not necessary except when unusual features present
- BCC vs. squamous cell carcinoma (SCC): BCC is **positive** for BerEP4

DIFFERENTIAL DIAGNOSIS

Squamous Cell Carcinoma (SCC)

- Most cases are easily separated; however, basosquamous type of BCC shows prominent squamous differentiation
 - Overlying actinic keratosis or Bowen disease often seen in association with SCC
 - Typical BCC features seen especially at tumor periphery
 - BerEP4 strongly **positive** in BCC
- Superficial shave biopsies may be impossible to accurately separate

Actinic Keratosis (AK)

- Can be difficult to separate in very superficial shave biopsies
 - AK typically shows basilar budding of atypical squamous cells and overlying parakeratosis
 - No mucinous stroma, peripheral palisading, or tumor-stromal retraction artifact should be seen
 - Numerous apoptotic and mitotic figures favor BCC

Merkel Cell Carcinoma

- Nodular to sheet-like proliferation of highly atypical basaloid cells
- Nuclei have "salt and pepper" chromatin or nuclear clearing
- **Positive:** CK-pan, CK20 (perinuclear dot-like); neuroendocrine markers, polyomavirus (MCPyV clone)

Sebaceous Carcinoma

- Can show prominent areas of basaloid differentiation
- Atypical multivacuolated cells with nuclear indentations should be present
- **Positive:** Androgen receptor (±BCC); CAM5.2, CK7; EMA (clear cells)

Adnexal Neoplasms

- On superficial biopsies, microcystic adnexal carcinoma and eccrine carcinomas may not be recognized
- May be prudent to diagnose basaloid neoplasm, with exclusion comment

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Merkel Cell Carcinoma

KEY FACTS

ETIOLOGY/PATHOGENESIS

- Recent studies have shown strong link to infection with polyomavirus

CLINICAL ISSUES

- Rare, highly aggressive tumors with greater metastatic potential than melanoma
- Typically occurs in sun-damaged skin of elderly
- More common in males
- Complete and wide excision and radiotherapy are most common treatments

MICROSCOPIC

- Highly atypical basaloid neoplasm composed of infiltrative cords, trabeculae, nodular and sheet-like areas
- Angiolymphatic invasion identified in high percentage of cases
- Typically dermal-based, but may show epidermal (pagetoid) involvement in up to 20% of cases

- Markedly increased mitoses and apoptotic bodies
- Areas of geographic necrosis often present, especially in larger tumors
- Nuclear crush artifact and streaming may be seen, similar to small cell carcinomas
- Basaloid cells with high N:C ratio, scant cytoplasm, large nuclei, granular to clear chromatin, and indistinct nucleoli

ANCILLARY TESTS

- Immunohistochemistry is important in confirming diagnosis and excluding metastatic carcinoma
- MCC is typically **positive** for keratins, including CK20, with perinuclear dot-like staining and neuroendocrine markers

TOP DIFFERENTIAL DIAGNOSES

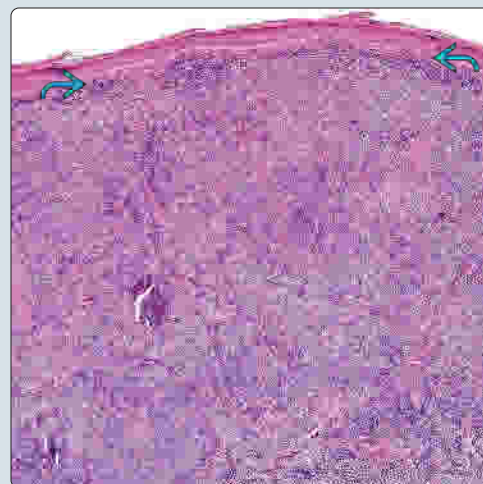
- Basal cell carcinoma, metastatic small cell carcinoma (especially lung origin)
- Small round blue cell tumors: Melanoma, lymphoma, Ewing sarcoma, rhabdomyosarcoma

Clinical Photograph of MCC

(Left) Clinical photograph of Merkel cell carcinoma (MCC) shows a well-circumscribed, erythematous dermal nodule. (Courtesy J. Wu, MD.) (Right) Low magnification of MCC shows diffuse dermal involvement by sheets and nodules of atypical basaloid cells. There is a thin grenz zone separating the tumor from the epidermis [2].

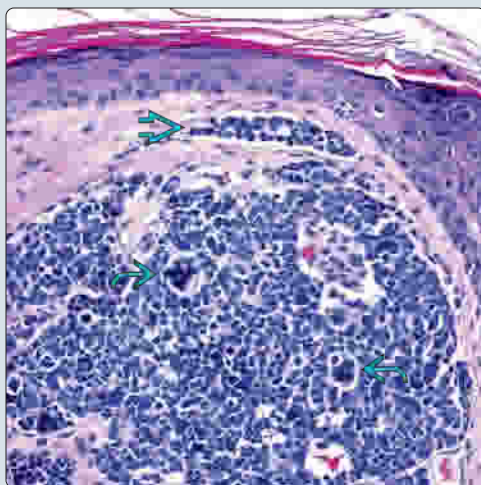


Dermal Sheets and Nests of Basaloid Cells

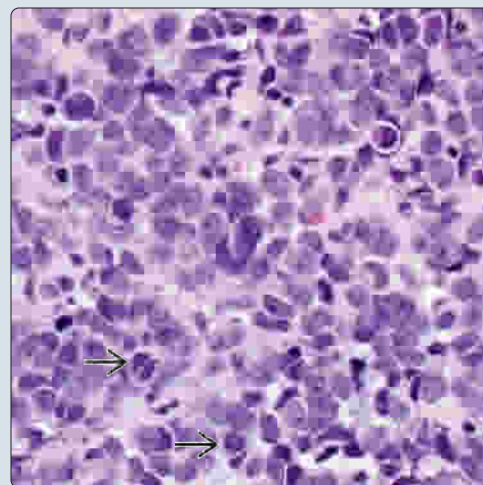


Superficial Dermal Portion of MCC

(Left) The superficial dermal portion of this tumor shows enlarged, atypical basaloid cells with several atypical mitotic figures [2]. Invasion of a superficial lymphatic vessel is also seen [2], a finding more commonly identified at the periphery of the tumor. (Right) The cells seen here are intermediate, but with a very high nuclear to cytoplasmic ratio. The chromatin is delicate, with a salt and pepper appearance. Mitoses are easily identified throughout the tumor [2].



Salt and Pepper Nuclear Chromatin



TERMINOLOGY

Abbreviations

- Merkel cell carcinoma (MCC)

Synonyms

- Cutaneous neuroendocrine carcinoma
- Primary small cell carcinoma of skin

Definitions

- Malignant neoplasm of cutaneous neuroendocrine cells

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Recent studies have shown strong link to infection with polyomavirus
 - Merkel cell polyoma virus infection is found in up to 90% of cases
- Associated with immunosuppression
 - Organ transplant and HIV(+) patients have much higher incidence

Cell of Origin

- Postulated to represent malignant transformation of cutaneous neuroendocrine (Merkel) cells or pluripotent stem cells, but this remains speculative

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare
- Age
 - Typically in elderly patients (> 65 years old)
- Sex
 - Male > female (2.5:1)
- Ethnicity
 - Caucasians much more commonly affected than other races

Site

- Sun-damaged skin
- Usually head and neck or extremities

Presentation

- Dermal nodular or plaque-like mass lesion
- Rapidly enlarging mass, possibly with ulceration &/or hemorrhage

Natural History

- Aggressive tumors with high incidence of local recurrence, lymph node and distant metastasis
- Clinical staging should include imaging studies, especially chest and abdominal CT scans

Treatment

- Surgical approaches
 - Complete and wide excision to ensure complete local removal
 - Consideration may be given to sentinel lymph node (SLN) biopsy

- However, SLN positivity does not seem to be very sensitive for regional lymph node involvement, as many patients progress to distant metastases

- Adjuvant therapy
 - Radiotherapy is generally used and may lead to remission in some cases
 - Chemotherapy is less effective and does not prolong overall survival

Prognosis

- High incidence of recurrence (up to 30%) and metastasis (up to 75%)
- Overall prognosis is poor
 - Death due to disease is high, even with treatment
 - Worse prognosis associated with advanced age, head and neck location, large size, and immunosuppression

MACROSCOPIC

General Features

- Nodular tumor with blue or red appearance

Size

- Typically < 2 cm

MICROSCOPIC

Histologic Features

- Highly atypical invasive basaloid neoplasm
 - Composed of infiltrative cords, trabeculae, nests, nodular and sheet-like areas
 - Associated dermal desmoplasia may be present
 - Enlarged, hyperchromatic basaloid tumor cells with high N:C ratio, scant cytoplasm, large nuclei, granular to clear (vesicular) chromatin, and indistinct nucleoli
 - Nuclear clearing is distinctive feature often seen
 - This finding is not present in basal cell carcinoma (BCC)
 - Mitotic figures are abundant
 - Typically, numerous apoptotic bodies
 - Areas of geographic necrosis often present, especially in larger tumors
 - Nuclear crush artifact and streaming may be seen, similar to small cell carcinoma
 - Angiolymphatic invasion identified in significant percentage of cases, often at periphery of tumor
 - Partial tumor regression may be present
- Typically dermal-based
 - May show epidermal (pagetoid) involvement in up to 20% of cases
 - Purely pagetoid (in situ) cases have been reported
- Areas of squamoid or adnexal (including follicular, ductal, or glandular) differentiation may be present in minority of cases
 - Rarely, melanocytic differentiation may be present
 - These findings suggest that MCC may arise from primitive pluripotential (stem) cell that can differentiate along multiple different lines, rather than specific neuroendocrine cell
- Rarely, spindle cell/sarcomatoid differentiation mimicking atypical fibroxanthoma (AFX), leiomyosarcoma, osteosarcoma, or rhabdomyosarcoma may be seen

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CK-PAN	Positive	Dot positivity	May or may not show dot-like positivity, but will be positive
CK20	Positive	Dot positivity	Rare cases may be negative
CK8/18/CAM5.2	Positive	Dot positivity	Most cases show dot reactivity
NSE	Positive	Cytoplasmic	Most cases are positive (but nonspecific marker)
Polyomavirus large T antigen	Positive	Nuclear	This marker for polyomavirus large T antigen has greater sensitivity and specificity than MCPyV antibody
Chromogranin-A	Positive	Cytoplasmic	Most cases are positive
Synaptophysin	Positive	Cytoplasmic	Most cases are positive
CK7	Negative	Dot positivity	Isolated cases may be CK7 positive when CK20 negative
S100	Negative		
HMB-45	Negative		
TTF-1	Negative		
CD45	Negative		
CD99	Negative		

ANCILLARY TESTS

Immunohistochemistry

- Immunohistochemistry (IHC) is important in confirming diagnosis and excluding metastatic neuroendocrine carcinoma
 - MCC is typically **positive** for keratins [CK-PAN, CK20, CK8/18 (CAM5.2)], often with perinuclear dot-like staining
 - Merkel cell polyomavirus (MCPyV) is detected in ~ 80%, but polyomavirus large T antigen is much more sensitive and specific (97%)

Genetic Testing

- Trisomy 6 is identified in many cases of MCC, up to 50% in some studies
- Deletion of short arm of chromosome 1 (1p36) is also commonly identified

DIFFERENTIAL DIAGNOSIS

Basal Cell Carcinoma (BCC)

- Most cases show areas of peripheral palisading, mucinous stroma, and tumor-stromal retraction artifact
- Less atypia and mitotic activity
- MCC should always be considered in high-grade/pleomorphic-appearing cases of BCC
- Positive:** EpCAM/BER-EP4/CD326; **negative:** CK20, chromogranin-A, & synaptophysin

Metastatic Small Cell Carcinoma

- Clinical history and complete examination important to exclude metastasis
- Especially lung origin, is **positive** for TTF-1 and nearly always **negative** for CK20
- Small cell carcinomas from other sites are usually TTF-1 **negative**

Small Cell Melanoma

- Rare variant of melanoma; typically see areas of associated junctional nesting and overlying pagetoid spread

- Cells show more abundant cytoplasm, prominent nucleoli, and may see cytoplasmic pigmentation and intranuclear pseudoinclusions
- S100 protein, SOX10, HMB-45, melan-A typically **positive**; **negative:** Cytokeratins, CK20, and neuroendocrine markers

Lymphoma

- Lymphomas are dyscohesive, lacking cord-like and trabecular growth pattern of MCC
- Various lymphoid markers, including CD45, will be **positive**
- CK20 and neuroendocrine markers **negative**

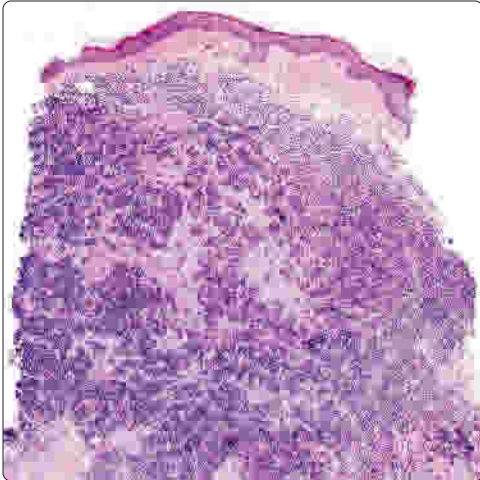
Small Round Blue Cell Tumors

- These tumors include neuroblastoma, Ewing/primitive neuroectodermal tumor (PNET), rhabdomyosarcoma
- Very rare in skin (typically metastatic from other sites); most cases occur in children
- Immunohistochemistry distinguishes from MCC

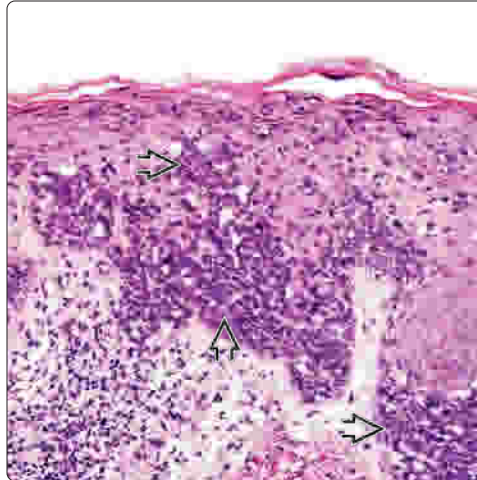
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Deeply Infiltrate Dermal Basaloid Tumor

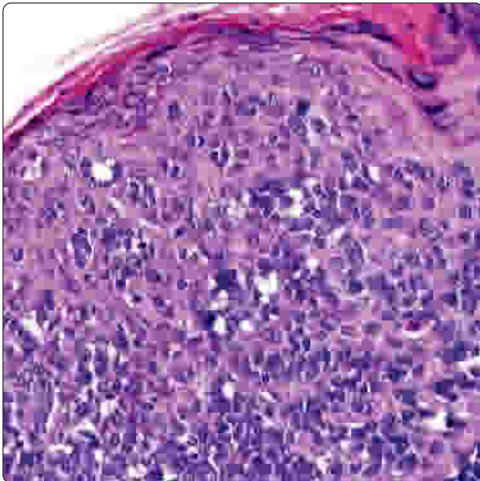


Pagetoid Extensions as Carcinoma In Situ

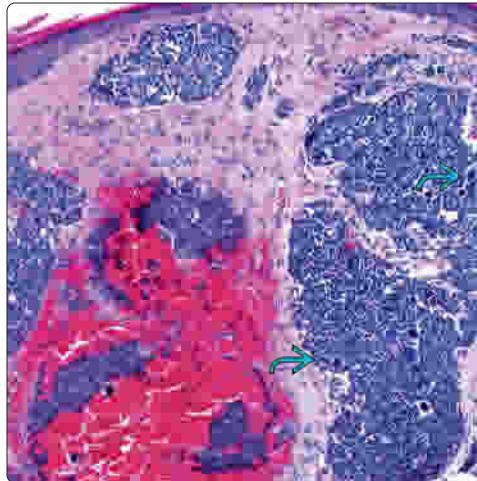


(Left) There is a zone of separation from the dermal-based tumor and the overlying surface epithelium. The tumor shows a destructive growth into the dermis, with a vague lobular appearance, but scant stromal tissue. (Right) Pagetoid intraepidermal spread of MCC is seen in a minority of cases (< 20%). No dermal component is present in this image.

Pagetoid MCC In Situ

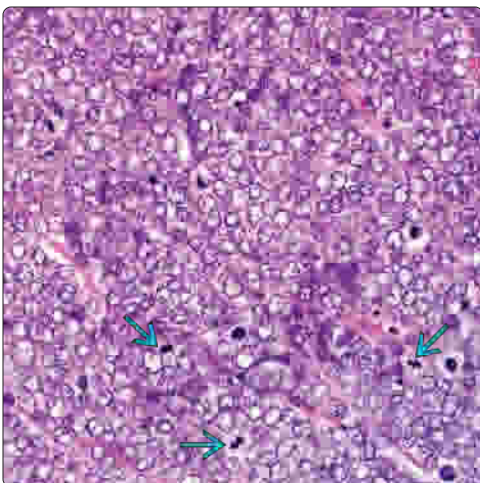


Superficial Dermal Portion of MCC

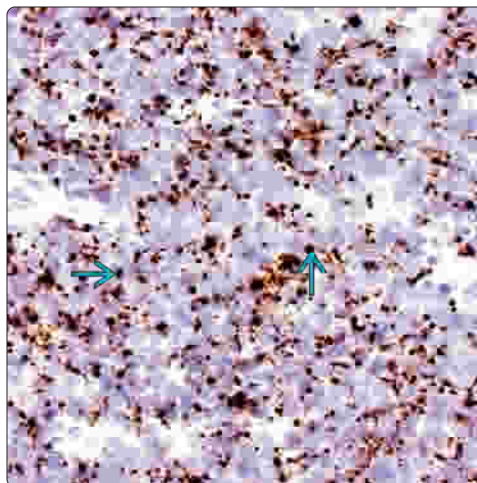


(Left) Uncommonly, a prominent full-thickness intraepidermal spread of atypical blue Merkel cells can be seen in MCC. Concurrent invasive tumor is usually identified. (Right) High magnification of the superficial dermal portion of this tumor shows enlarged, crowded and markedly atypical-appearing basaloid cells with several atypical mitotic figures easily identified.

Vesicular Nuclear Chromatin Appearance



CK20 Immunohistochemistry in MCC



(Left) High magnification of MCC shows nuclear molding, hyperchromasia, and vesicular-to open-appearing chromatin. Numerous apoptotic and mitotic figures are easily identified. (Right) CK20 immunohistochemistry shows cytoplasmic and perinuclear (Golgi) dot-like positivity. This pattern is not a feature identified in other basaloid tumors, helping to confirm the diagnosis.

Dermatofibrosarcoma Protuberans

KEY FACTS

TERMINOLOGY

- Low-grade malignant spindle cell tumor of skin characteristically showing prominent storiforming

CLINICAL ISSUES

- Typically occurs in young adults
- Male predominance
- Rarely occur on head and neck
- Dermal and subcutaneous nodular/multinodular or plaque-like mass
- Optimal treatment is complete surgical excision with negative margins
- Excellent prognosis in most cases
- Relatively low recurrence rate
- Very low metastatic rates (usually only in cases with fibrosarcomatous transformation)

MACROSCOPIC

- Polypoid, multinodular, or bosselated-appearing tumor

MICROSCOPIC

- Dermal and subcutaneous involvement
- Cells arrayed in storiform or cartwheel patterns
- Proliferation of monomorphic spindle-shaped cells
- Lesional cells lack significant pleomorphism
- Mitoses usually infrequent (< 4/10 HPF)
 - Atypical mitoses usually absent

ANCILLARY TESTS

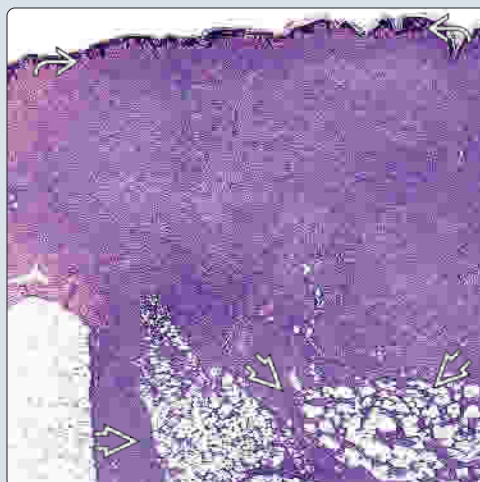
- CD34 is most reliable marker, typically strongly and diffusely **positive**

TOP DIFFERENTIAL DIAGNOSES

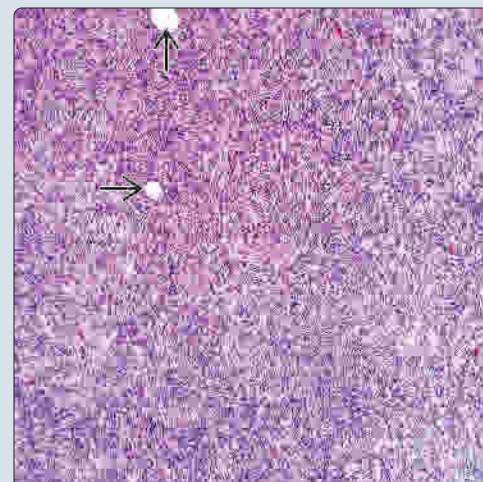
- Cellular dermatofibroma/fibrous histiocytoma
- Fibrosarcoma (including transformation in DFSP)
- Spindle cell/desmoplastic melanoma
- Desmoid fibromatosis
- Leiomyosarcoma

Low Magnification of DFSP

(Left) Low magnification of a DFSP shows deep dermal and subcutaneous involvement by a cellular spindle cell tumor with fat entrapment. Epidermis is separated from tumor by thin grenz zone. (Courtesy T. Mentzel, MD.) **(Right)** Cellular and more atypical area of DFSP shows a proliferation of densely packed atypical spindle cells with storiforming. A few adipocytes are surrounded (entrapped) by the neoplastic population.

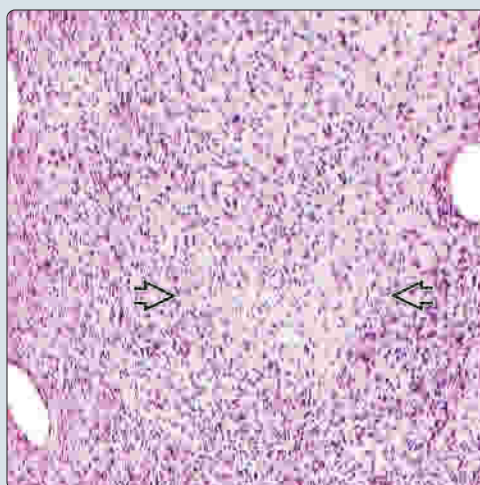


Fat Entrapment Within DFSP

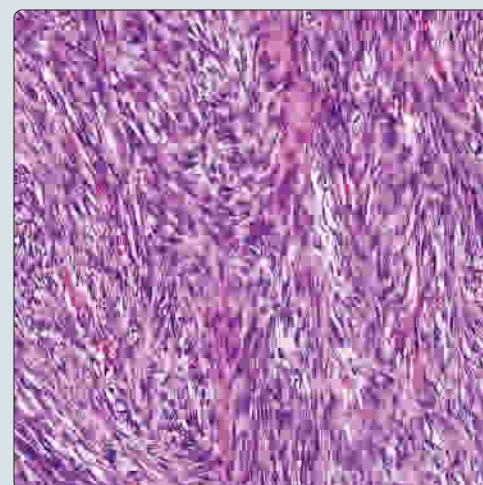


DFSP With Myxoid Stroma

(Left) Areas of myxoid stromal change may be seen in a minority of cases of DFSP. The myxoid changes give a lighter stromal appearance to a tumor that is otherwise usually quite densely cellular. **(Right)** Higher power view of a cellular DFSP shows a neoplastic proliferation arranged in a storiform pattern, composed of monomorphous spindle cells. Cellular atypia and pleomorphism are mild.



DFSP With Prominent Storiforming



TERMINOLOGY

Abbreviations

- Dermatofibrosarcoma protuberans (DFSP)

Synonyms

- Bednar tumor (pigmented DFSP)

Definitions

- Low-grade malignant spindle cell tumor of skin characteristically showing prominent storiforming

ETIOLOGY/PATHOGENESIS

Unknown in Most Cases

- Rare cases reportedly associated with previous trauma, burns, or arsenic exposure

Genetics

- Rearrangements of collagen 1A1 (*COL 1A1*)/platelet-derived growth factor B (*PDGFB*)
- Characteristic t(17;22) detected in most cases
 - Can be detected by FISH or PCR studies for fusion protein

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon tumors
- Age
 - Typically occurs in young adults
- Sex
 - Male predominance

Site

- Rarely occur on head and neck
 - Most often present on trunk or extremities

Presentation

- Dermal and subcutaneous nodular/multinodular or plaque-like mass
- Slowly progressive, locally aggressive tumor

Treatment

- Optimal treatment is complete surgical excision with negative margins
- In cosmetically sensitive areas, combined approach with dermal regenerative template, sub-atmospheric pressure and skin graft has been suggested
- Imatinib has been used for locally extensive and metastatic disease

Prognosis

- Excellent in most cases
- Local recurrences in up to 30% of cases (tumors with positive margins much more likely to recur)
- Very low metastatic potential (and essentially only in cases with fibrosarcomatous transformation)

IMAGING

General Features

- MR shows DFSP to be T2-hyperintense with marked enhancement
- T2 hyperintense and demonstrates marked enhancement

MACROSCOPIC

General Features

- Polypoid, multinodular, or bosselated-appearing tumor
 - Rare cases may be atrophic appearing
- Cut surface usually gray-white
- May show hemorrhage and cystic changes

Size

- Range: 1-10 cm

MICROSCOPIC

Histologic Features

- Spindle cell tumor with deep dermal and subcutaneous involvement
- Proliferation of monomorphic spindle-shaped cells
- Arrayed in storiform or cartwheel patterns
- Lesional cells typically lack significant atypia and pleomorphism
 - Elongated spindle-shaped nuclei
 - Mild nuclear hyperchromasia, small to inconspicuous nucleoli
 - Moderate amounts of eosinophilic cytoplasm
- Mitoses are usually infrequent (< 4/10 HPF) and are not atypical
 - Increased mitoses and atypical forms are seen with fibrosarcomatous change
- Necrosis is usually absent
- Adnexal structures entrapped or entombed (not obliterated)
- Subcutaneous areas typically show "honeycombing" fat entrapment
- Myxoid stromal change may be prominent in some cases

Variants

- **Bednar tumor**
 - Pigmented DFSP due to intratumoral population of benign melanocytes
 - No prognostic significance
- **Giant cell fibroblastoma (GCFB)**
 - Clinical: Occurs in children and young adults
 - Histologic features are distinctive
 - Proliferation of spindled cells and giant cells with nuclear hyperchromasia
 - Pseudovascular spaces lined by giant cells
 - Mutations involving *COL 1A1/PDGFR* (same as in DFSP)

ANCILLARY TESTS

Immunohistochemistry

- Useful to confirm diagnosis, although often not necessary
 - CD34 is most reliable marker with a strong and diffuse reaction
 - May be weak and focal in some cases

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CD34	Positive	Cell membrane & cytoplasm	Usually strongly and diffusely positive
FXIIIA	Negative		May see focal staining of scattered single cells
CD68	Negative		May see focal staining of entrapped histiocytes
CD163	Negative		Strongly positive in dermatofibroma
S100	Negative		Rarely positive in pigmented cells (Bednar tumor)
CK-PAN	Negative		
p63	Negative		

- FXIIIA is usually **negative** (**positive** in dermatofibroma [DF])
 - May show focal staining, usually at periphery or in scattered dendritic cells
- CD68, CD10, lysozyme, and chymotrypsin are typically **negative**
 - These markers are relatively nonspecific (but **positive** in DF and atypical fibroxanthoma)
- S100 rarely can be **positive** in a few (dendritic) cells
 - Will highlight pigmented cells in Bednar tumor
 - Will be **positive** in entrapped adipocytes

Genetic Testing

- t(17;22): Rearrangement of collagen 1A1 (*COL 1A1*)/platelet-derived growth factor B (*PDGFB*)

DIFFERENTIAL DIAGNOSIS

Cellular Dermatofibroma/Fibrous Histiocytoma

- More pleomorphic cell types
 - Both small spindle-shaped fibroblastic cells and larger histiocytoid-appearing cells
- No prominent storiforming
- May show superficial, jagged involvement of fat
 - No deep, honeycombing fat entrapment as in DFSP
- **Negative:** CD34; **positive:** FXIIIA, CD68, CD163, CD10
 - CD34 may be focally **positive**, usually at periphery

Fibrosarcoma (Including Transformation in DFSP)

- Areas of increased cellularity, atypia, and mitoses (> 5/10 HPF)
- Spindle cells typically arrayed in prominent fascicles with herringbone appearance
 - Intersecting fascicles at 45° angles
- Usually see loss of CD34 expression in fibrosarcomatous areas

Fibromatosis

- Proliferation of elongated spindle cells associated with dense collagenous stroma
- Small blood vessels (parallel to direction of fibroblasts) associated with extravasated erythrocytes
- Often deeply infiltrates soft tissues but lacks honeycombing fat entrapment of DFSP
- **Positive:** β -catenin, SMA; **negative:** CD34

Solitary Fibrous Tumor

- More common in soft tissues; only rarely occurs in skin

- Composed of patternless proliferation of spindle cells associated with thickened, ropy collagen bundles and staghorn vessels
- **Positive:** CD34 but lacks storiforming of DFSP

Leiomyosarcoma

- Long fascicles of enlarged, atypical, eosinophilic-staining spindle cells
- Usually shows more cytologic atypia, pleomorphism, and multiple mitoses
- Lacks storiforming pattern of DFSP
- **Positive:** Desmin, actins; **negative:** CD34 (typically)

Atypical Fibroxanthoma (AFX)

- Occurs in sun-damaged skin of elderly
- Dermal-based proliferation of markedly atypical and pleomorphic-appearing tumor cells
- Usually shows mixture of highly atypical spindle-shaped and epithelioid cells with tumor giant cells, lacking storiform pattern

Spindle Cell/Desmoplastic Melanoma

- Typically shows greater atypia, pleomorphism, and nuclear hyperchromasia, without storiforming
- Overlying melanoma in situ present in majority of cases (> 70%)
- **Positive:** S100 protein, SOX10; other melanocytic markers often **negative**

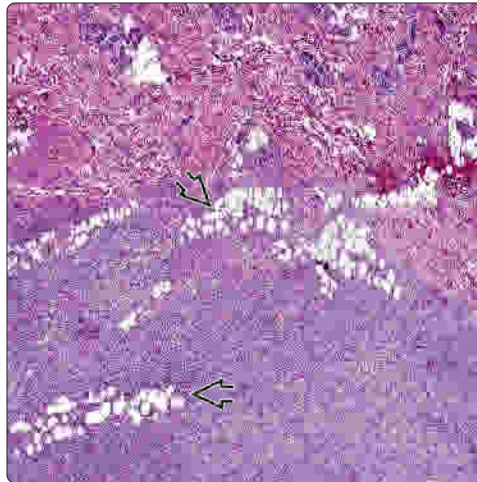
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Multinodular Growth in Clinical Image of DFSP

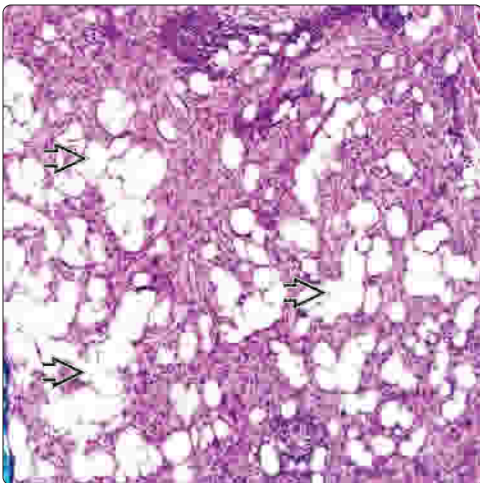


Prominent Honeycombing Fat Entrapment

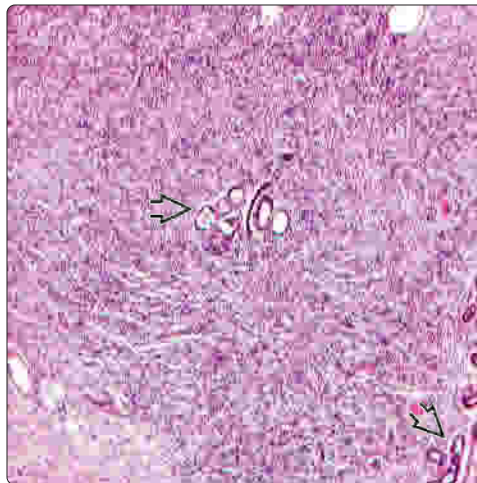


(Left) Dermatofibrosarcoma protuberans (DFSP) is often characterized clinically by an exophytic, multinodular growth with areas of interposed flattening or atrophy. (Right) Deep dermal and subcutaneous involvement by a DFSP shows prominent honeycombing fat entrapment. The neoplasm is cellular, giving a blue appearance to the proliferation on low power. The borders of the tumor are irregular.

Prominent Fat Entrapment

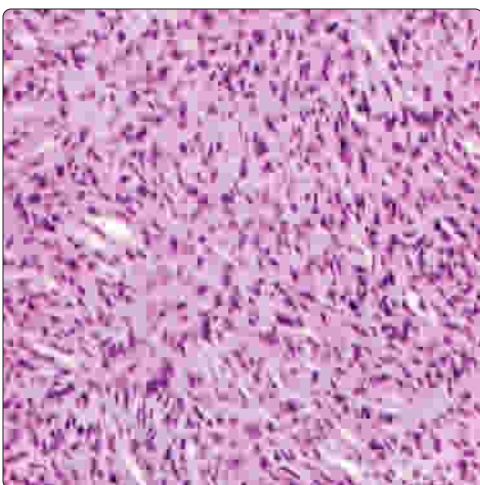


Entrapped Skin Adnexal Glands

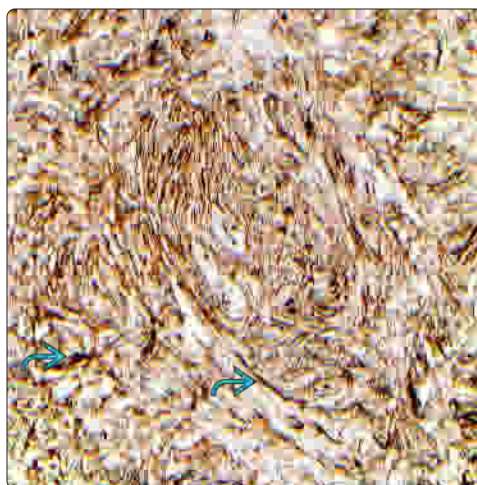


(Left) The deep subcutaneous tissues of this DFSP highlight the significant fat entrapment. The neoplastic cells are cytologically bland, and mitotic figures are not easily identified. (Right) On low power, there are a number of adnexal glands that are entrapped by the cellular, vaguely storiform neoplastic proliferation. However, there is no tumor destruction of these adnexal structures.

Spindled Population in DFSP



CD34 Immunohistochemistry in DFSP



(Left) High power of DFSP shows a proliferation of bland spindle cells, lacking marked pleomorphism or anaplasia. Mitotic figures are often difficult to identify. (Right) Strong immunohistochemical staining for CD34 is shown in nearly all of the tumor spindle cells in a typical DFSP. Vessels will also be highlighted with the stain, an appropriate internal control.

Ceruminous Adenocarcinoma

KEY FACTS

TERMINOLOGY

- Malignant neoplasm derived from ceruminous glands of external auditory canal

CLINICAL ISSUES

- Rare neoplasm
- Mean: 49 years; range: 21-92 years
- Female > male (1.5:1)
- Outer 1/3-1/2 of external auditory canal
- Pain, hearing loss (sensorineural or conductive), tinnitus
- Wide, radical complete surgical excision, especially when adenoid cystic carcinoma

MACROSCOPIC

- Mean: 1.4 cm; range: 0.5-3.0 cm

MICROSCOPIC

- Tumor necrosis (comedonecrosis) diagnostic of carcinoma
- Perineural invasion, if present, helps define malignancy

- Ceroid (cerumen) pigment **absent** in malignancies
- Separated into 3 tumor types
 - Ceruminous adenocarcinoma
 - Ceruminous adenoid cystic carcinoma (ACC)
 - Ceruminous mucoepidermoid carcinoma (CMEC)
- Infiltrative into soft tissue, between benign ceruminous glands, and bone
- Nuclear pleomorphism with prominent nucleoli
- Easily identified mitotic figures, including atypical forms

ANCILLARY TESTS

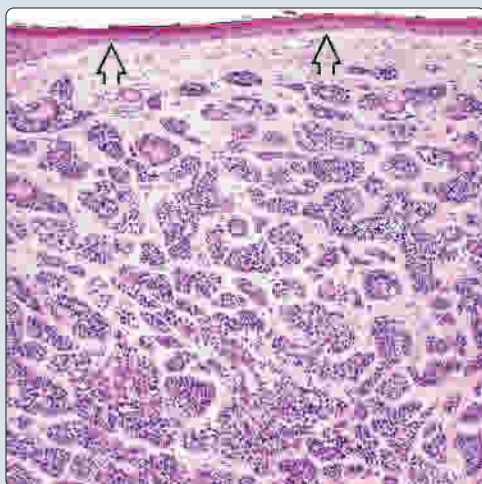
- Highlights biphasic nature of tumor
 - Luminal cells: CK7, CD117
 - Basal cells: p63, S100 protein, and CK5/6

TOP DIFFERENTIAL DIAGNOSES

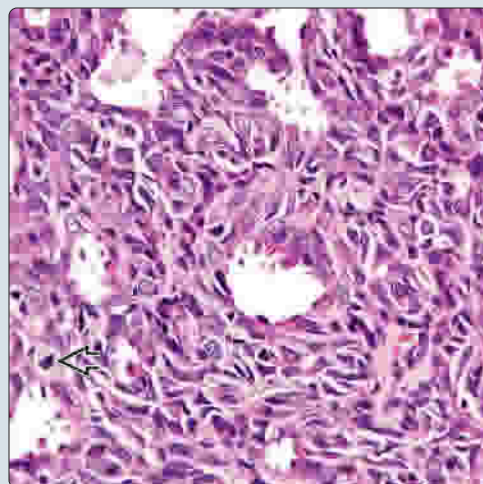
- Parotid gland primary (ACC or MEC) must be excluded
- Ceruminous adenoma
- Neuroendocrine adenoma of middle ear

Surface Overlying Ceruminous Adenoid Cystic Carcinoma

(Left) Hematoxylin and eosin shows uninvolved surface epithelium with an infiltrative mixture of patterns in this ceruminous adenoid cystic carcinoma (ACC). There are isolated ceruminous glands just below the surface. (Right) Hematoxylin and eosin shows markedly pleomorphic neoplastic proliferation with apocrine snouts, biphasic appearance, and mitotic figures in this ceruminous adenocarcinoma, not otherwise specified.

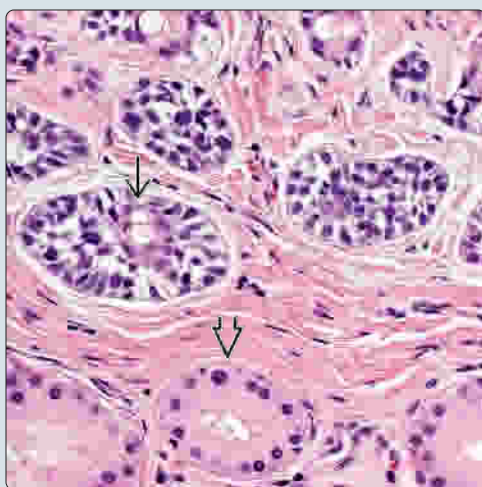


Pleomorphism in Ceruminous Adenocarcinoma, Not Otherwise Specified

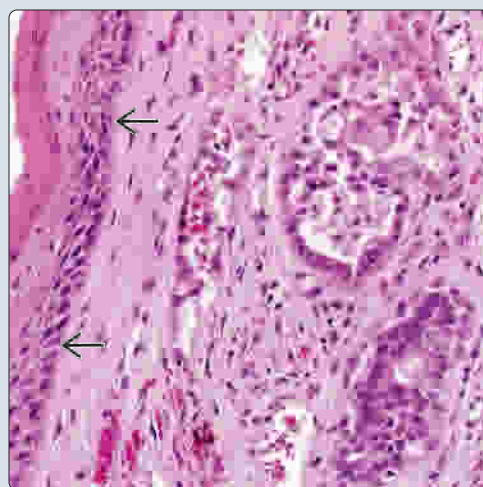


ACC Adjacent to Benign Ceruminous Glands

(Left) Hematoxylin and eosin shows native ceruminous glands adjacent to neoplastic glands with ceruminous differentiation in this ceruminous ACC. Cerumen glands in the background help to confirm the origin of the tumor. (Right) The surface epithelium is intact and separate from the neoplastic ceruminous proliferation. There is a blending of epidermoid, transitional and mucocytes within this ceruminous carcinoma, mucoepidermoid type.



Ceruminous Mucoepidermoid Carcinoma



TERMINOLOGY

Synonyms

- Ceruminous adenocarcinoma, cylindroma, ceruminoma
 - Ceruminous adenocarcinoma, not otherwise specified
 - Ceruminous adenoid cystic carcinoma (ACC)
 - Ceruminous mucoepidermoid carcinoma (CMEC)

Definitions

- Malignant neoplasm derived from ceruminous glands of external auditory canal

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare neoplasm: < 2.5% of all external ear neoplasms
- Age
 - Mean: 49 years; range: 21-92 years
- Sex
 - Female > male (1.5:1)

Site

- Outer 1/3-1/2 of external auditory canal

Presentation

- Pain is most common symptom
- Hearing loss (sensorineural or conductive), tinnitus
- Slowly growing polypoid mass, often in posterior canal
- Drainage, discharge, or bleeding, with occasional surface ulceration

Treatment

- Surgical approaches
 - Wide, radical complete surgical excision, especially when adenoid cystic carcinoma
- Radiation
 - Employed for ceruminous adenocarcinoma and mucoepidermoid carcinoma but usually only palliative

Prognosis

- Good, although ~ 50% of patients die from disease within 3-10 years of presentation
- Recurrences are common, especially if positive surgical margins or ceruminous ACC

IMAGING

General Features

- Defines extent of tumor
- **Excludes** direct extension from parotid gland or nasopharyngeal tumor

MACROSCOPIC

Size

- Mean: 1.4 cm; range: 0.5-3.0 cm

MICROSCOPIC

Histologic Features

- Separated into 3 tumor types
 - Ceruminous adenocarcinoma, not otherwise specified
 - ACC

- CMEC
- Infiltrative into soft tissue, between benign ceruminous glands, and bone
- Tumor may secondarily involve surface mucosa
- Cellular, arranged in solid, cystic, cribriform, glandular, and single cell patterns
- Tumor necrosis (comedonecrosis) and perineural invasion diagnostic of carcinoma
- Nuclear pleomorphism with prominent nucleoli
- Easily identified mitotic figures (3/10 HPF), including atypical forms
 - ACC tends to have fewer mitotic figures
- Desmoplastic stroma between neoplastic epithelial islands
- Ceroid (cerumen, wax) pigment **absent** in malignancies
- Must **exclude** parotid gland primary MEC or ACC with direct extension into EAC

Margins

- Must be free of tumor to achieve better long-term prognosis

ANCILLARY TESTS

Immunohistochemistry

- Highlights biphasic nature of tumor
 - Luminal cells: CK7, CD117
 - Basal cells: p63 (nuclear), S100 protein (cytoplasmic and nuclear), and CK5/6

DIFFERENTIAL DIAGNOSIS

Parotid Gland Primary

- Direct extension, especially by adenoid cystic carcinoma
- Must be excluded either clinically or radiographically

Ceruminous Adenoma

- Circumscribed, noninfiltrative, dual cell population with cerumen granules present

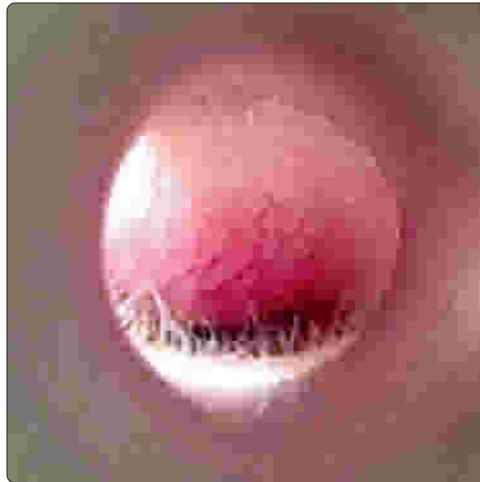
Neuroendocrine Adenoma of Middle Ear

- Neuroendocrine and epithelial neoplasm with multiple patterns, delicate salt and pepper nuclear chromatin, and chromogranin and synaptophysin (+)

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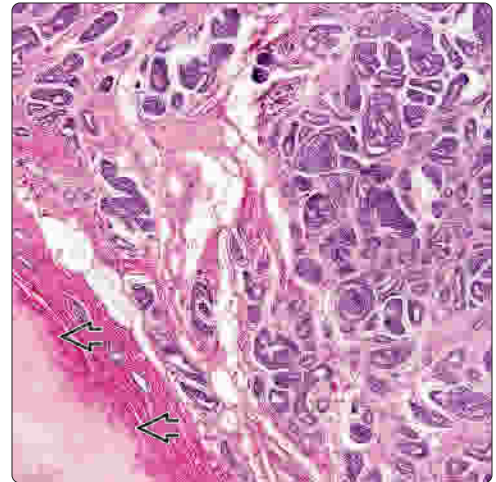
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Otoscopic View of Ceruminous Adenocarcinoma

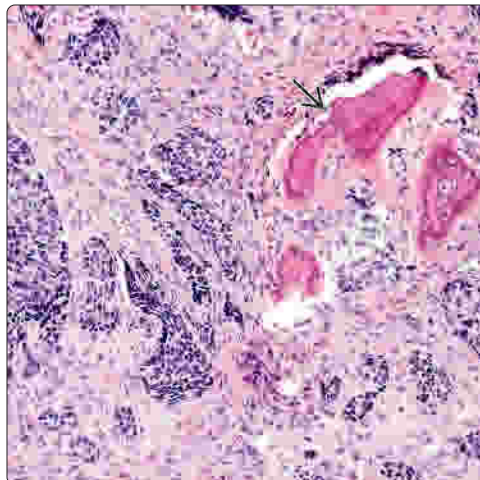


(Left) An otoscopic view of a right ear canal ceruminous adenocarcinoma. Note the erythema of the epithelium. (Courtesy J. Fowler, PA.) **(Right)** Hematoxylin and eosin shows invasion to the cartilage by a glandular proliferation in this ceruminous adenocarcinoma, not otherwise specified. Note the haphazard glandular proliferation.

Ceruminous Adenocarcinoma Near Cartilage

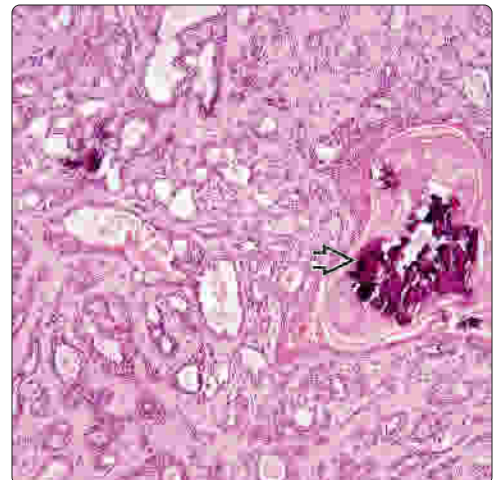


Bone Destruction by Ceruminous Adenoid Cystic Carcinoma

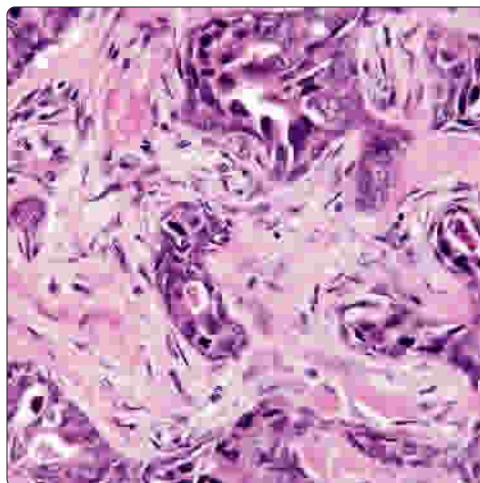


(Left) There are isolated fragments of destroyed bone in this ceruminous ACC. It is not uncommon to have the bones of the canal destroyed by the neoplasm. **(Right)** Hematoxylin and eosin demonstrates a cellular neoplasm, focally showing squamous differentiation and calcification in this ceruminous adenocarcinoma, not otherwise specified. A desmoplastic stroma is present.

Ceruminous Adenocarcinoma, Not Otherwise Specified, With Calcification

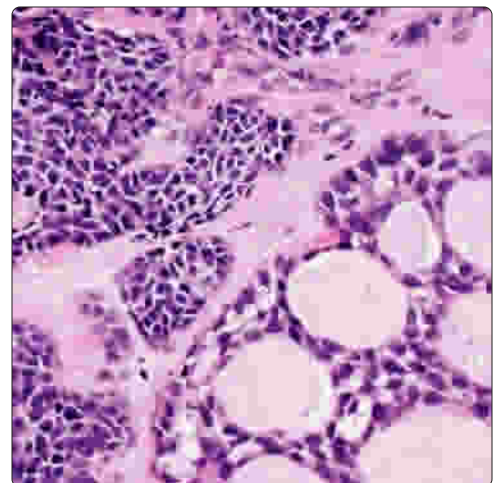


Pleomorphism of Biphasic Tumor

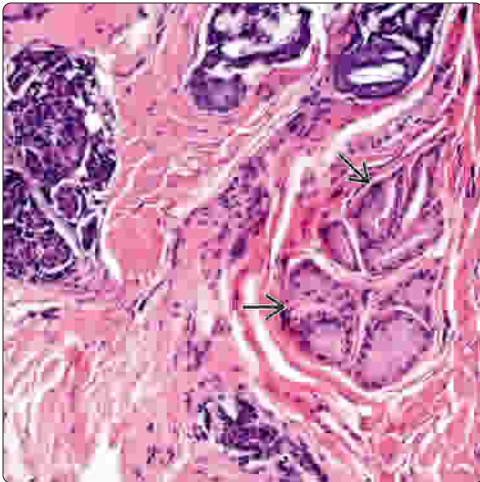


(Left) There is remarkable pleomorphism of the cells with apocrine snouting in the glandular cells of this ceruminous adenocarcinoma, not otherwise specified. Nuclear hyperchromasia is prominent. **(Right)** A solid pattern and a more characteristic cribriform pattern is seen in this ceruminous ACC. Basophilic material within the pseudocysts is glycosaminoglycans. Reduplicated basement membrane material is in continuity with the stroma.

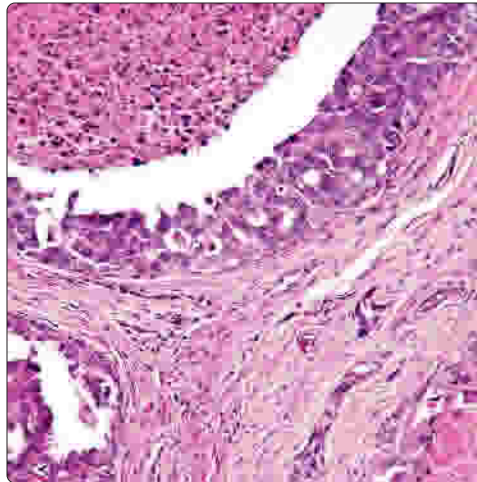
Ceruminous Adenoid Cystic Carcinoma Patterns



Ceruminous Glands and Carcinoma Islands

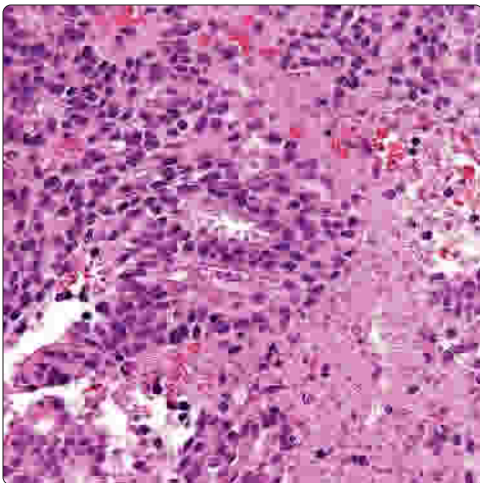


Comedonecrosis in Adenocarcinoma

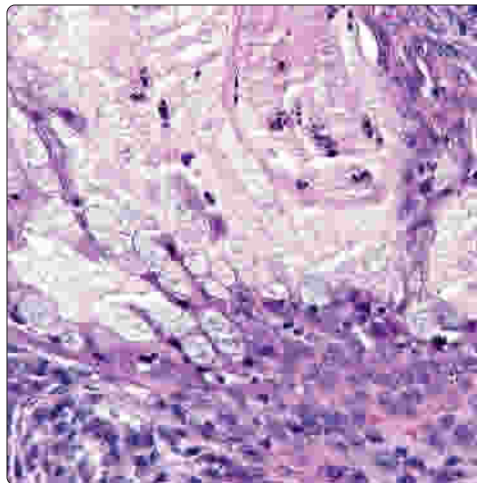


(Left) The native ceruminous glands are surrounded by a neoplastic proliferation of atypical glandular epithelium. The ceruminous glands help to confirm the origin of the tumor. **(Right)** A comedo-type necrosis is visible within a markedly pleomorphic epithelium. Comedonecrosis is not common but helps to define malignancy in ceruminous neoplasms when present.

Tumor Necrosis in Ceruminous Adenocarcinoma, Not Otherwise Specified



Ceruminous Mucoepidermoid Carcinoma

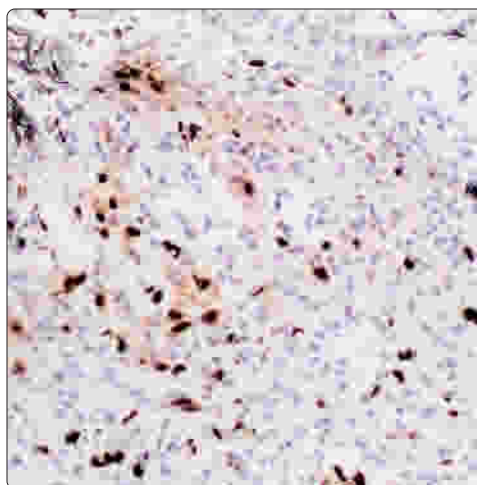


(Left) Hematoxylin and eosin shows a glandular pattern with necrosis in this ceruminous adenocarcinoma, not otherwise specified. There is only mild nuclear pleomorphism in this field. **(Right)** Hematoxylin and eosin reveals a mucoepidermoid carcinoma showing squamoid to transitional epithelium containing mucocytes. A parotid gland primary must always be excluded before yielding a definitive diagnosis.

CK5/6 Highlights Basal and Luminal Cells



Ki-67 Labels Increased Number of Mitoses



(Left) CK5/6 shows basal immunoreactivity in this gland of a ceruminous adenocarcinoma. Weaker reactivity is noted in the luminal cells. **(Right)** An immunohistochemistry for Ki-67 may highlight an increased number of mitoses in a carcinoma. In general, mitoses are easily identified on standard H&E stained material.

Rhabdomyosarcoma

KEY FACTS

TERMINOLOGY

- Primitive malignant tumor with histologic and phenotypic features of embryonic skeletal muscle

CLINICAL ISSUES

- Most common soft tissue sarcoma in children
- Young people: Embryonal; adults: Alveolar
- Female ~ male
- Ear:** Unilateral, refractory otitis media, deafness, otalgia
 - Embryonal rhabdomyosarcoma (RMS) is most common in ear
- Sinonasal tract:** Obstruction, mass, proptosis, discharge
 - Alveolar RMS is most common in sinuses, nose, throat (SNT)
- Often mismanaged as infection or aural polyp initially
- Wide local excision combined with multimodality therapy
- Relative good prognosis: 60% 5-year survival overall
 - Age, stage, anatomic site, and histologic subtype dependent

MACROSCOPIC

- Polypoid mass, often with intact epithelial surface

MICROSCOPIC

- Primitive mesenchymal cells with rhabdomyoblasts: Eccentric, eosinophilic cytoplasm
- Cytoplasmic eosinophilia with tadpole, elongated cytoplasmic extensions

ANCILLARY TESTS

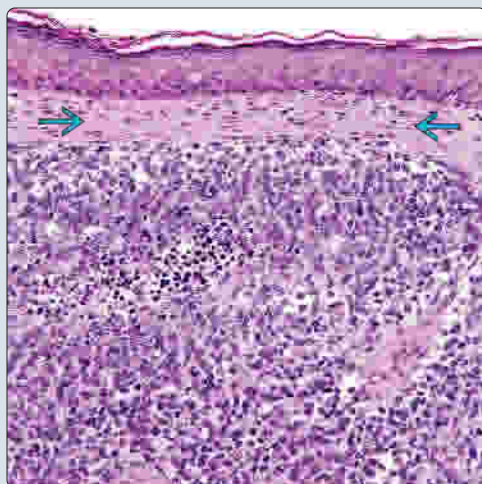
- Positive:** Muscle markers; alveolar RMS: *FOXO1* gene fusions

TOP DIFFERENTIAL DIAGNOSES

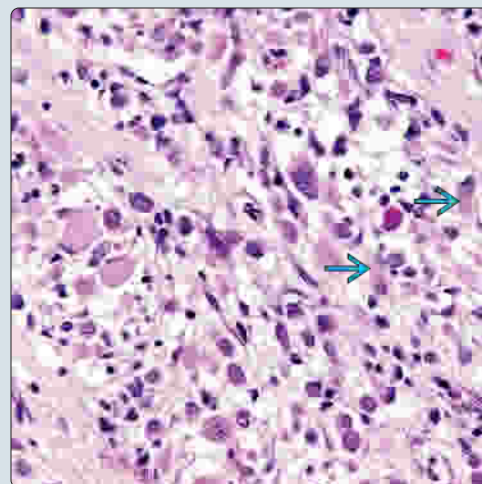
- Aural polyp, fetal rhabdomyoma, melanoma, lymphoma, olfactory neuroblastoma, sinonasal undifferentiated carcinoma, neuroendocrine carcinoma, PNET/Ewing sarcoma, pituitary adenoma, mesenchymal chondrosarcoma, teratocarcinosarcoma

Embryonal Rhabdomyosarcoma of External Auditory Canal

(Left) This aural rhabdomyosarcoma (RMS) shows an intact surface squamous epithelium with a grenz zone between the primitive mesenchymal cells and the surface. This small round blue cell pattern is common in embryonal RMS. (Right) Embryonal RMS with rhabdomyoblasts shows primitive cells with eccentric, eosinophilic cytoplasm. Cytoplasmic extensions create elongated or tadpole cells. The stroma is myxoid to edematous.

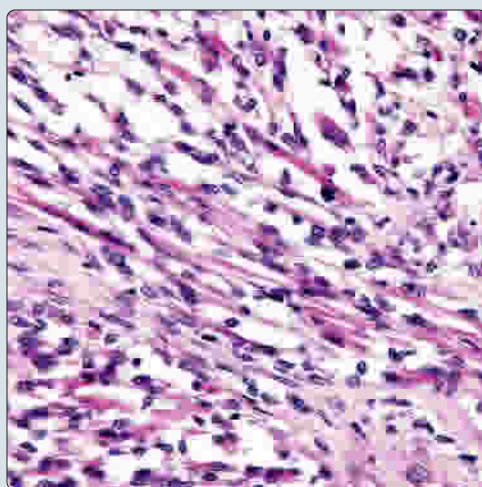


Rhabdomyoblasts With Eccentric Nuclei

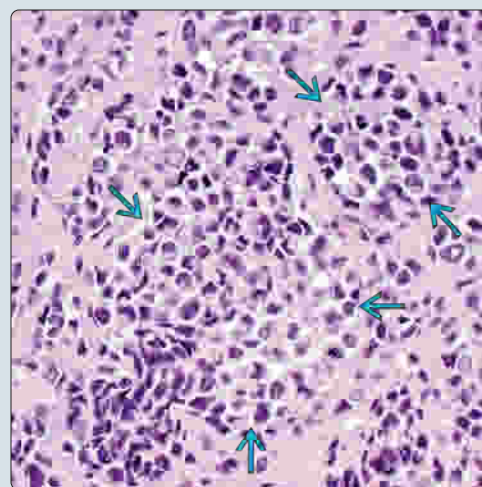


Fascicular Arrangement

(Left) There is a fascicular arrangement to this RMS. The cells are stellate, showing remarkably elongated cytoplasmic extension. A few cells have cross striations, but they are difficult to detect without special studies or oil magnification. (Right) An alveolar RMS shows a vague alveolus with cells adherent at the periphery and then showing central degeneration or a dilapidated appearance. Note the remarkable eccentric, eosinophilic cytoplasm.



Alveolar Rhabdomyosarcoma



TERMINOLOGY

Abbreviations

- Rhabdomyosarcoma (RMS)

Synonyms

- Embryonal rhabdomyosarcoma
 - Includes spindle, botryoid, and pleomorphic variants
- Alveolar rhabdomyosarcoma
 - Includes spindle, botryoid, and pleomorphic variants

Definitions

- Primitive malignant mesenchymal tumor with skeletal muscle differentiation

ETIOLOGY/PATHOGENESIS

Syndrome Association

- RMS is increased in Li-Fraumeni (*TP53* inactivating mutation); Costello syndrome (*HRAS* mutation); Beckwith-Wiedemann (11p15.5 alteration)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Most common soft tissue sarcoma in children and adolescents
 - Most common soft tissue sarcoma in head and neck
 - Embryonal RMS is most common in ear
 - Alveolar RMS is most common in sinonasal tract
- Age
 - Young people (usually < 20 years)
 - **Embryonal** subtype most frequently
 - Adults may be affected, but less common
 - **Alveolar** > embryonal subtype
- Sex
 - Female ~ male
- Ethnicity
 - Increased incidence in white people vs. black people

Site

- Sites affected (order of frequency)
 - **Head and neck**
 - Orbit and eyelid > oropharynx > parotid > ear (auditory canal and middle ear) > nasopharynx, nasal cavity, paranasal sinuses
 - Botryoid type arises beneath mucosal membrane
 - Urogenital tract > extremities (arms, legs)

Presentation

- **Ear:** Unilateral, refractory otitis media, deafness, otalgia, sanguinous/bloody discharge, mass
- **Sinonasal tract (SNT):** Obstruction, pain, mass, proptosis, discharge, epistaxis, neurologic symptoms

Treatment

- Options, risks, complications
 - Often mismanaged as infection or aural polyp initially
 - Diagnose early to prevent temporal bone destruction and meningeal involvement
 - Complications of treatment include

- Facial growth retardation, intellectual retardation, neuroendocrine dysfunction (hypothyroidism), intracranial bleed
- Visual changes, dental problems, hearing loss, esophageal stenosis
- Delayed effects of chondronecrosis
- Second malignancy

- Surgical approaches
 - Wide local excision **must** be included in management protocol
- Adjuvant therapy
 - Multiagent chemotherapy
- Radiation
 - Used specifically to manage local disease, combined with chemotherapy

Prognosis

- Considered systemic disease by definition
 - Most tumors present as pT2 lesions
 - Highly aggressive neoplasm with rapid expansion into adjacent structures
- Relatively good: ~ 60% 5-year survival overall
 - Depends on age, stage, anatomic site, and histologic subtype
 - 80% 5-year survival for group I patients
 - Anatomic site prognosis: Head and neck > genitourinary > extremities > retroperitoneum
 - Smaller tumors tend to behave better
 - Embryonal has better prognosis than alveolar subtype
- *PAX7-FOXO1A* tumors: Younger patients, less locally aggressive, seem to have better prognosis than *PAX3-FOXO1A* tumors

IMAGING

General Features

- Used to delineate extent of disease for staging purposes
- Expansile soft tissue mass with heterogenous signals showing mixture of stroma, necrosis, and vascularity

MACROSCOPIC

General Features

- Polypoid mass, often with intact, smooth epithelial surface
- Poorly circumscribed, fleshy pale tan mass
- Spindle cell tumors are more fibrous and firm with whorled cut surface

Size

- Usually small (< 2.5 cm), anatomic site dependent

MICROSCOPIC

Histologic Features

- Embryonal and alveolar are most common types
- Usually intact surface epithelium
- Primitive spindled mesenchymal cells in fascicles and whorls
- Rhabdomyoblasts (eccentric, eosinophilic cytoplasm) rare
- Stellate cells with round nuclei
- Cytoplasmic eosinophilia with tadpole, elongated cytoplasmic extensions
- Cross striations are uncommon and difficult to identify

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
Vimentin	Positive	Cytoplasmic	All tumor cells
Myogenin	Positive	Nuclear	All tumor cells (also Myf-4)
MYOD1	Positive	Nuclear	Myoblast determination protein 1 (MYOD1)
MITF	Positive	Nuclear	All tumor cells
Desmin	Positive	Cytoplasmic	Most tumor cells (eccentric)
Actin-HHF-35	Positive	Cytoplasmic	Most tumor cells are positive
Actin-sm	Positive	Cytoplasmic	
Myoglobin	Positive	Cytoplasmic	
Myosin	Positive	Cytoplasmic	
CD56	Positive	Cell membrane and cytoplasm	Many cases will have strong, positive reaction
CK-PAN	Positive	Dot positivity	~ 5% of cases, usually isolated cells
CD45RB	Negative		
Chromogranin-A	Negative		However, synaptophysin may be positive in some tumors
HMB-45	Negative		
SOX10	Negative		Negative with S100 protein, SOX10, and GFAP

- Multinucleation may be seen
- Myxoid background stroma is common
- Necrosis may be noted
- Botryoid variant has cambium layer
 - Increased cellularity immediately below intact surface, then hypocellular deeper into stroma

ANCILLARY TESTS

Cytology

- Smears used as triage for ancillary studies (immunohistochemistry, FISH analysis)
- Cellular smears with small blue round cell with plasmacytoid rhabdomyoblasts
- Lacks lymphoglandular bodies and cellular cohesion

Histochemistry

- PAS diastase highlights cytoplasmic glycogen

Immunohistochemistry

- Muscle markers **positive**

In Situ Hybridization

- Alveolar RMS shows *FOXO1A* gene fusions with *PAX3* or *PAX7*
 - *FOXO1A*: Forkhead box O1 (previously *FKHR*) at chromosome 13q14.1
 - *PAX3*: Paired box homeotic gene 3 (2q35)
 - *PAX7*: Paired box gene 7 (1p36.2-p36.12)
 - Translocations generate *PAX3-FOXO1A* [t(2;13)(q35;q14)] and *PAX7-FOXO1A* [t(1;13)(p36;q14)] gene fusions
- FISH break-apart probe most easily detects *FOXO1A* fusion
- Spindle cell RMS show *NCOA2* rearrangements

DIFFERENTIAL DIAGNOSIS

Otic (Aural) Polyp

- Plasma cells and lymphocytes within stroma, but no atypia

Fetal Rhabdomyoma

- Young age, spindle cell proliferation with gradient of cellularity, lack of cytologic atypia, muscle differentiation

Small Round Blue Cell Tumors

- Melanoma, lymphoma, olfactory neuroblastoma, sinonasal undifferentiated carcinoma, neuroendocrine carcinoma, PNET/Ewing sarcoma, pituitary adenoma, mesenchymal chondrosarcoma, teratocarcinosarcoma
- Anatomic site, histology, immunohistochemistry, and molecular features help with separation
- **Melanoma**: Pagetoid spread, pigment, pleomorphism; **positive**: S100 protein, SOX10, HMB-45
- **Lymphoma**: Atypical dyscohesive lymphoid cells; B- or T-cell restricted
- **Ewing sarcoma**: Small cells, coarse chromatin, necrosis; **positive**: CD99, Erg, FLI-1; **negative**: muscle markers
- **Teratocarcinosarcoma**: Primitive, teratoma-like mixture of carcinoma, sarcoma, and blastema-like elements; RMS may represent sarcoma

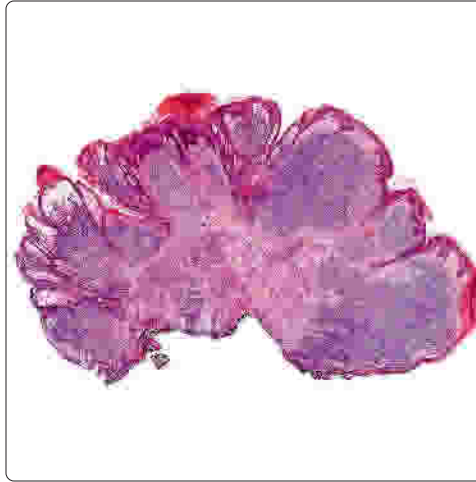
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MR of Masticator Space Rhabdomyosarcoma

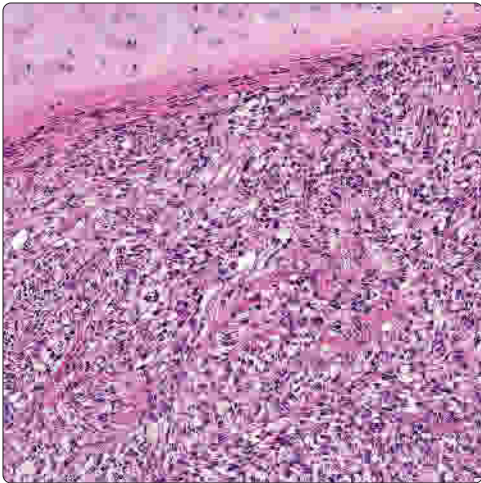


Polypoid Projections of Aural Rhabdomyosarcoma

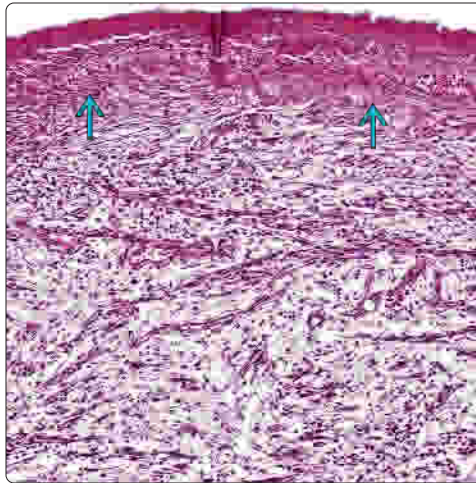


(Left) Axial MR T1WI (post contrast) shows slightly heterogeneous enhancement of a RMS identified in the ear and masticator space. This finding is nonspecific but does delineate the extent of the tumor. (Right) Rhabdomyosarcomas are frequently polypoid masses, often with an intact epithelial surface. This was an aural "polyp" identified in the external auditory canal.

Pericartilaginous Infiltration

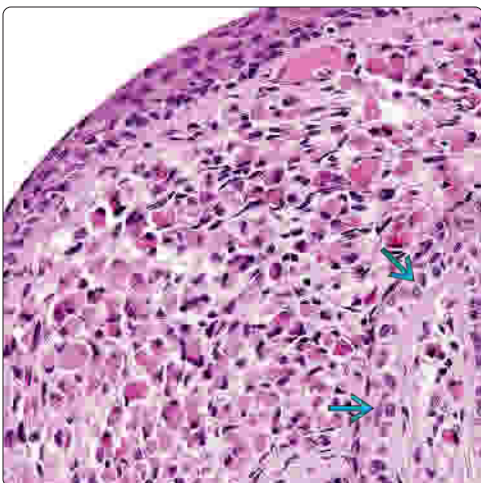


Cambium Layer Below Surface

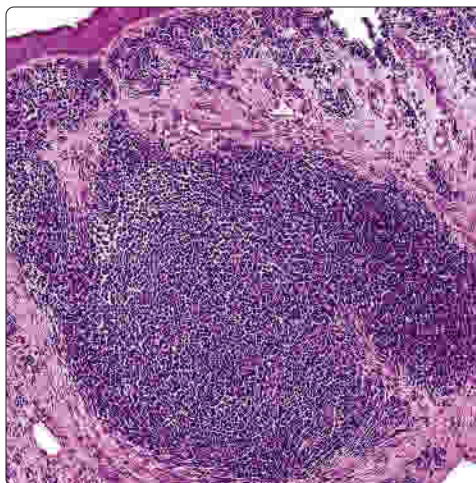


(Left) Tumors are frequently infiltrative, seen here expanding into the cartilage lining the external auditory canal space. Intratumoral fibrosis is noted in this embryonal RMS. The cells are primitive, arranged in a random fashion. (Right) The surface epithelium seen here is intact, overlying this botryoid variant of embryonal RMS. There is a cambium layer (increased cellularity) immediately below an intact surface, overlying a gradient of cellularity, which becomes more hypocellular as it goes deeper. The stroma is myxoid.

Rhabdoid Cells Below Surface Epithelium



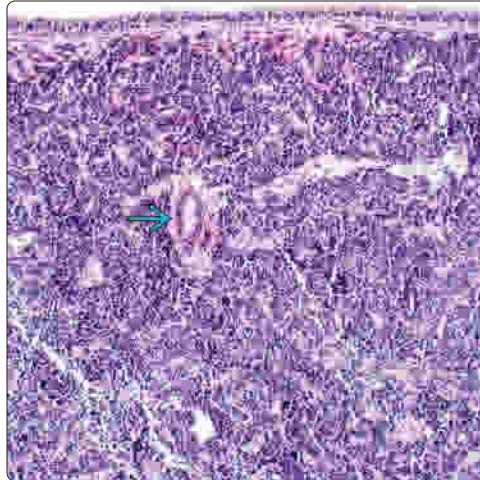
Small Blue Round Cell Population



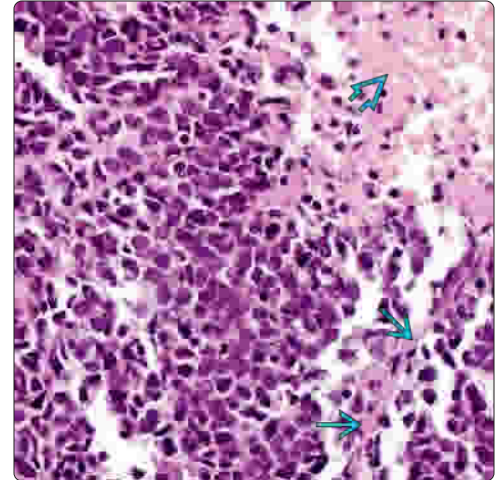
(Left) The epidermis seen here is intact, subtended by a sheet-like distribution of rhabdomyoblasts that shows eccentric, eosinophilic cytoplasm around dark nuclei. An uninvolved ceruminous gland is present. (Right) An intact surface epithelium subtended by a primitive mesenchymal population with a small round blue cell appearance is shown. These changes are similar to a chronic inflammation at this power of magnification.

Sheets of Neoplastic Cells

(Left) There is a primitive cell population filling the subepithelial space, arranged in a sheet-like to solid appearance. Note the isolated gland [red box] completely surrounded by tumor. (Right) This alveolar RMS is comprised of small blue round cells that are seen falling off the scaffolding [red box] of the stroma. Tumor necrosis [red box] is present, a finding that is not common in head and neck tumors.

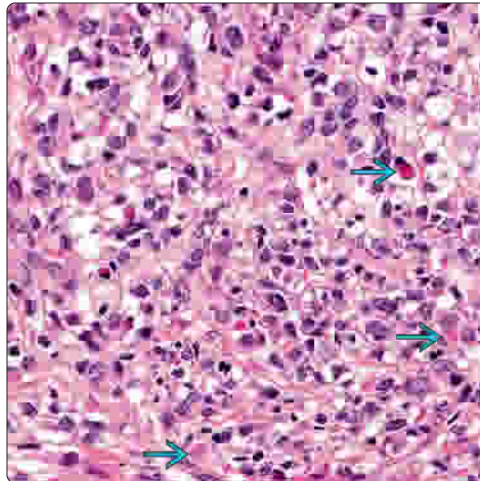


Tumor Comedonecrosis

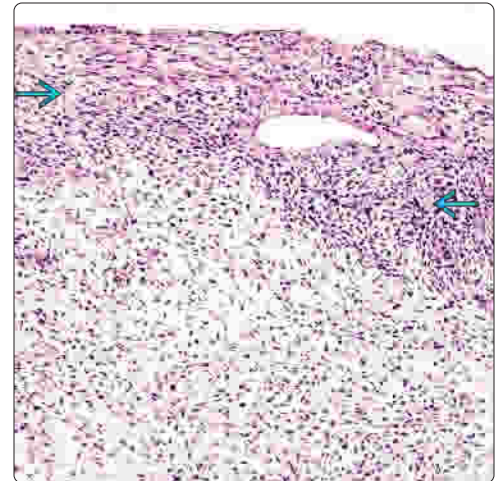


Eccentric Cytoplasm With Mitoses

(Left) These primitive mesenchymal cells are arranged in a haphazard pattern. However, there is pleomorphism and increased mitoses. Eccentric cytoplasm is noted [red box]. This type of tumor benefits from immunohistochemistry studies. (Right) There is an increased cellularity of primitive mesenchymal cells seen here just below the surface [red box], while a more myxoid or loose appearance is noted in the deeper layers of the tumor.

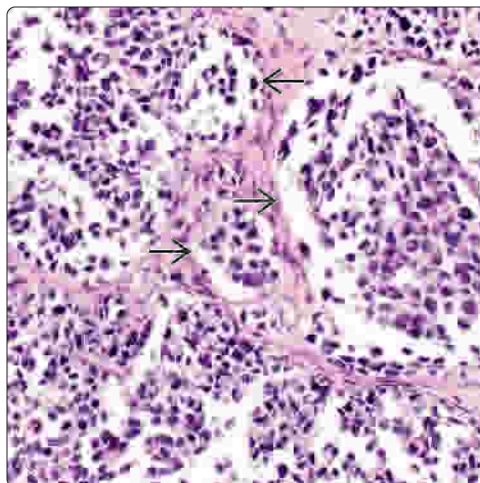


Cambium Layer Below Surface

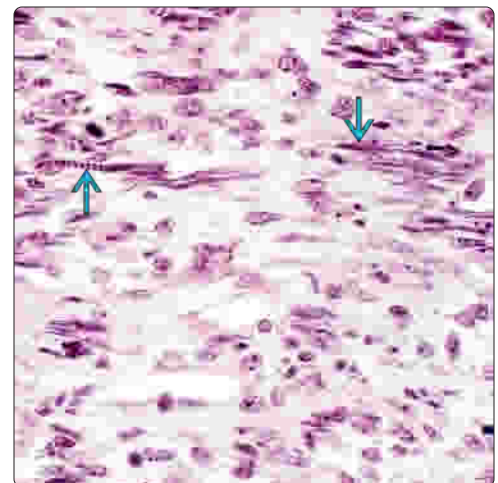


Alveolar Rhabdomyosarcoma

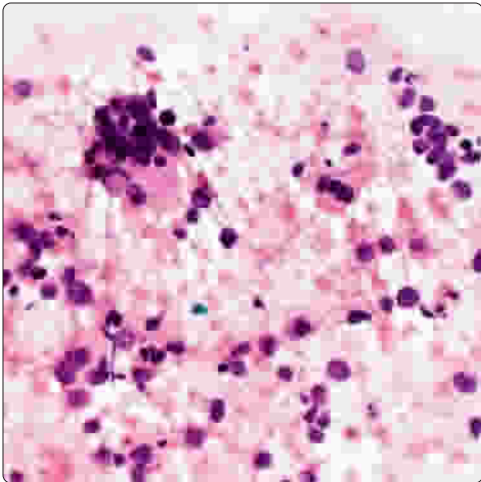
(Left) An alveolar RMS shows a vague alveolus [red box] with cells adherent at the periphery and then showing central degeneration or a dilapidated appearance. Note the eccentric, eosinophilic cytoplasm. (Right) The identification of strap cells [red box] in a RMS helps to confirm the diagnosis of skeletal muscle differentiation. However, strap cells may be seen in fetal rhabdomyoma also.



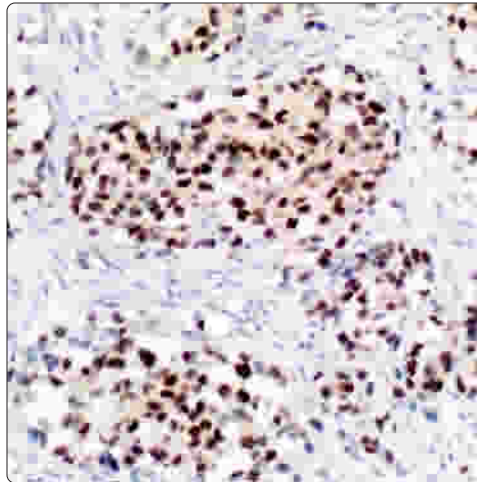
Strap Cells in Rhabdomyosarcoma



FNA Smear of Rhabdomyosarcoma

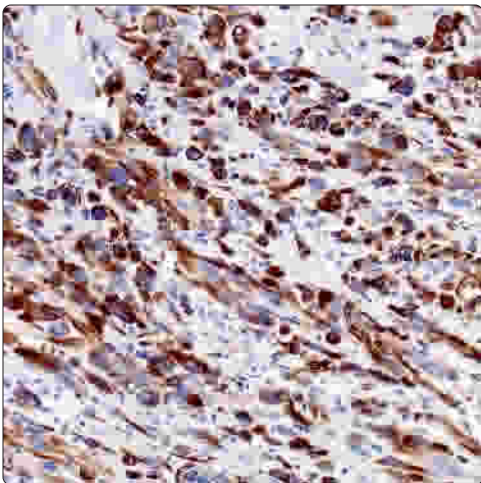


Nuclear Myogenin Positive Reaction

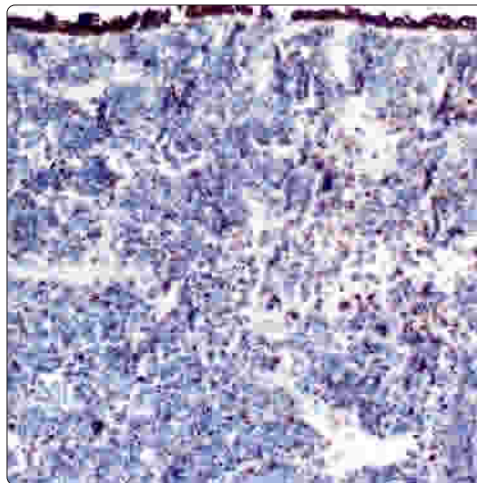


(Left) FNA smears are cellular, showing small dyscohesive aggregates of small blue round cells and eccentric cytoplasm focally. The background here is degenerated, but lacks lymphoglandular bodies or lymphoid tangles. (Right) The neoplastic cells of a RMS will show a strong and diffuse reaction with various muscle markers. Myogenin (shown) and MYOD1 usually give a strong and diffuse nuclear reaction.

Cytoplasmic Desmin Reactivity

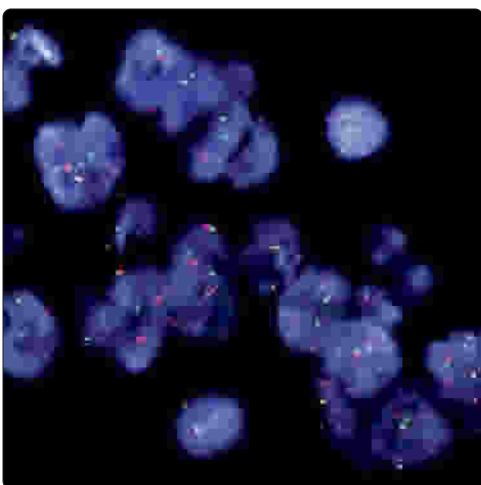


Dot-Like Keratin Reactivity in RMS

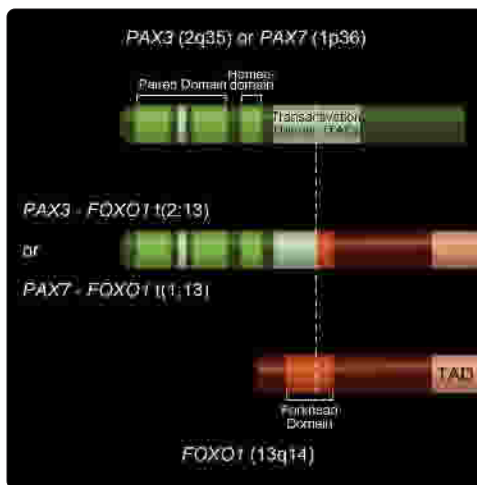


(Left) There is frequent variability in reactivity with the muscle markers used to confirm the diagnosis of RMS. Note that not all of the tumor cells are reactive with desmin. However, the pattern of reaction highlights the eccentric or tadpole cytoplasm. (Right) Up to 5-8% of RMS cases will show a dot-like (Golgi pattern) reaction with CK-PAN, as seen in this alveolar RMS. It is important to have targeted and pertinent IHC panels when evaluating small round blue cell neoplasms.

FOXO1 Break-Apart Probe for RMS



Fusion Sites for FOXO1 and PAX3 or PAX7



(Left) FISH shows rearrangement of the FOXO1 gene. Two probes (green and orange) in the Vysis LSI break-apart probe show rearrangement is present by detecting green and orange signals, rather than the yellow signal identified in normal cells that lack the translocation. (Right) This diagrammatic representation shows the breakpoints and subsequent fusion sites between the FOXO1 (previously FKHR) (13q14) region and either PAX3 (2q35) or PAX7 (1p36) transactivation domain region.

Metastatic/Secondary Tumors

KEY FACTS

TERMINOLOGY

- Tumors that secondarily involve ear &/or temporal bone, which originate from, but are not in continuity with, primary malignancies of other sites

CLINICAL ISSUES

- Uncommon (< 2% of all malignancies of ear and temporal bone) in surgical pathology
- Older ages, correlated with increased malignancies of other anatomic sites
- Presentation is late in disease course
 - Most are asymptomatic
- Usually bilateral, multiple, and include other bones
- Middle ear most frequently
 - Petrous apex most common site (~ 80%)
 - Mastoid bone, internal auditory canal
- Excision is performed for symptomatic relief
- Prognosis matches underlying disease but usually part of disseminated disease

MACROSCOPIC

- Lytic or blastic depending on tumor type, often large

MICROSCOPIC

- Most common tumors are carcinomas
 - Breast (~ 25%)
 - Lung (~ 10%)
 - Prostate (~ 10%)



ANCILLARY TESTS

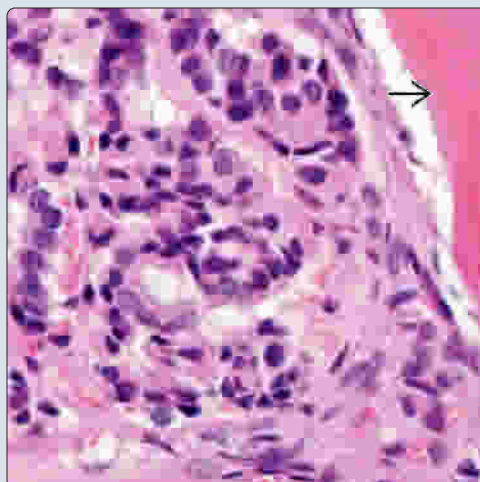
- Pertinent and targeted antibodies used to confirm metastatic disease

TOP DIFFERENTIAL DIAGNOSES

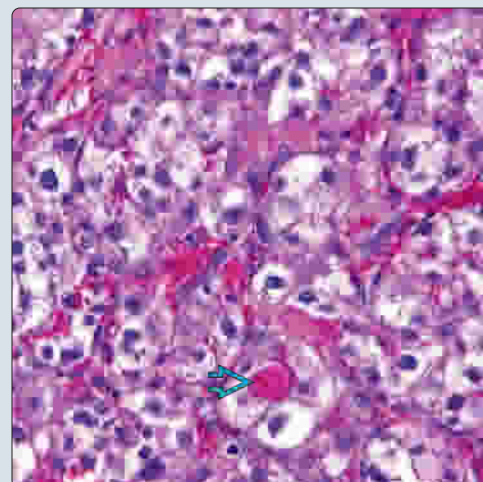
- Direct extension must be excluded
 - Salivary gland (parotid), eustachian tube, nasopharynx, posterior fossa of brain, skin
- **Primary tumors:** Neuroendocrine adenoma of middle ear, squamous cell carcinoma, primary middle ear adenocarcinoma

Metastatic Breast Carcinoma

(Left) Hematoxylin & eosin shows back-to-back glands within a stroma adjacent to spicules of bone  in this example of metastatic breast carcinoma. Obviously, other adenocarcinomas may show a similar histologic appearance. **(Right)** Hematoxylin & eosin shows glands with erythrocytes within pseudolumen , with a pseudoalveolar pattern of metastatic renal cell carcinoma. PAX8, renal cell carcinoma, and selected keratins may help to confirm the source of the primary tumor.

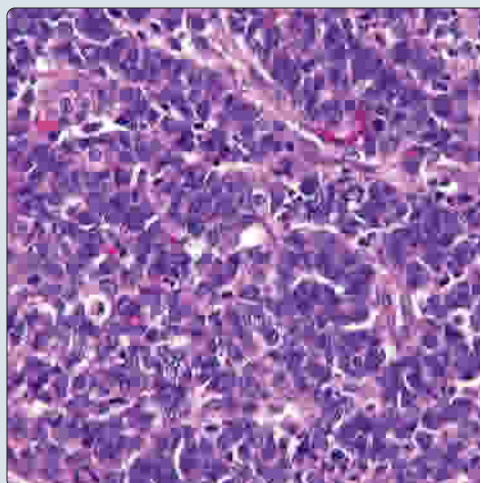


Metastatic Renal Cell Carcinoma

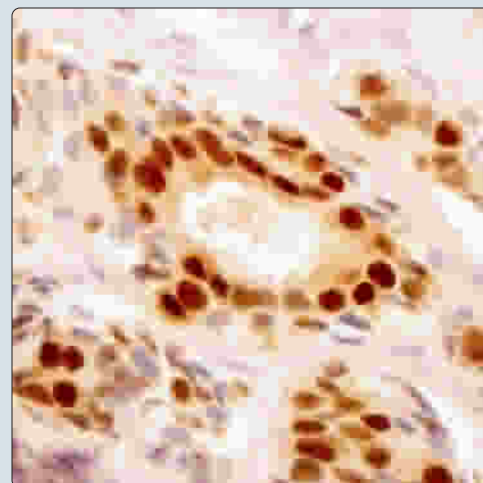


Metastatic Colon Adenocarcinoma

(Left) There are back-to-back glands seen here that are lined by columnar cells in a metastatic colon adenocarcinoma. Further positive reactivity with CDX-2 and CK20 would help to confirm the diagnosis. **(Right)** The estrogen receptor shows strong and diffuse nuclear reactivity within glandular profiles. This helps to support a diagnosis of metastatic breast carcinoma.



Strong Estrogen Reaction in Breast Cancer



TERMINOLOGY**Synonyms**

- Secondary tumors

Definitions

- Tumors that secondarily involve ear &/or temporal bone, which originate from, but are not in continuity with, primary malignancies of other sites
 - Some include direct continuity in this definition
 - Lymphomas and leukemias are excluded by definition

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Uncommon (< 2% of all malignancies of ear and temporal bone) in surgical pathology
 - Up to 20% in autopsy studies performed on cancer patients with disseminated disease
- Age
 - Older ages, correlated with increased malignancies of other anatomic sites
- Sex
 - Female > male (but tumor-type dependent)

Site

- Usually bilateral, multiple, and include other bones
- Petrous apex most common site (~ 80%)
- Mastoid bone, internal auditory canal, and middle ear

Presentation

- Asymptomatic
 - Most common (~ 1/3 of patients)
- Presentation is late in disease course
- Changes in hearing
- Dizziness, tinnitus
- Facial palsy and otalgia
- Otorrhea, mass

Treatment

- Rarely, may be isolated metastases
- Excision is performed for symptomatic relief

Prognosis

- Matches underlying disease but usually part of disseminated disease

MACROSCOPIC**General Features**

- Lytic or blastic lesion depending on tumor type

Size

- Variable but may be quite large

MICROSCOPIC**Histologic Features**

- Vascular/lymphatic metastases have different profile than direct extension
- Specific tumor type dictates histology
- Most common tumors are carcinomas
 - Breast (~ 25%)

- Lung (~ 10%)
- Prostate (~ 10%)
- Melanoma (~ 6%)
- Mesenchymal tumors rarely metastasize to ear and temporal bone
- Direct extension via eustachian tube, posterior fossa of skull, and external ear from parotid gland area
 - Upper aerodigestive tumors most common

ANCILLARY TESTS**Immunohistochemistry**

- Pertinent and targeted antibodies used to confirm metastatic disease

DIFFERENTIAL DIAGNOSIS**Direct Extension**

- Direct extension from salivary gland, nasopharynx, brain, or skin needs to be excluded
 - In general, this can be achieved by
 - Clinical history
 - Radiographic studies
 - Architectural and histologic features
 - Immunohistochemistry
 - Molecular studies

Primary Tumor

- Ear primaries may mimic metastatic tumors
 - Neuroendocrine adenoma of middle ear
 - Squamous cell carcinoma
 - Primary middle ear adenocarcinoma (aggressive papillary adenocarcinoma)

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Endolymphatic Sac Tumor

KEY FACTS

TERMINOLOGY

- Papillary epithelial neoplasm arising within endolymphatic sac associated with von Hippel-Lindau syndrome

CLINICAL ISSUES

- Endolymphatic sac or endolymphatic duct
- Symptoms usually present for years, suggesting slow tumor growth
- Mean age: 30-40 years; wide range
- Stigmata of von Hippel-Lindau in other organs: Kidney, pancreas, cerebellum
- Posterior petrous bone: Intraosseous vestibular aqueduct portion or operculum of endolymphatic duct/sac system

IMAGING

- T1-weighted images show hyperintensity (hypervascularity) of heterogeneous mass

MICROSCOPIC

- Up to 10 cm

- Bone invasion and remodeling
- Simple, coarse, broad papillary projections within cystic spaces
- Single layer of low cuboidal to columnar cells
- Clear to slightly eosinophilic, granular cytoplasm with indistinct cell borders/membranes

ANCILLARY TESTS

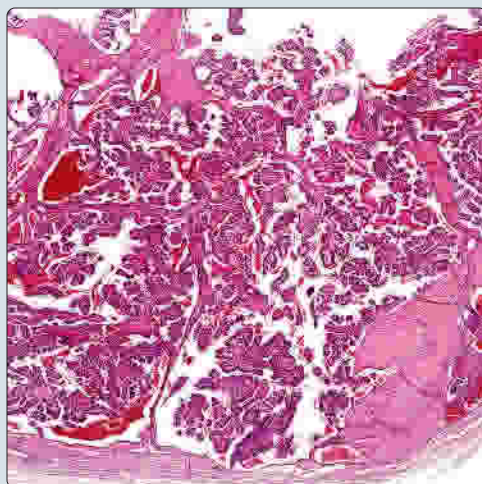
- Epithelial markers are usually **positive**

TOP DIFFERENTIAL DIAGNOSES

- Neuroendocrine adenoma of middle ear
- Paraganglioma
- Choroid plexus papilloma
- Metastatic renal cell carcinoma
- Metastatic papillary thyroid carcinoma
- Middle ear adenocarcinoma
- Ceruminous adenoma

Complex Papillary Tumor

(Left) Low-power view demonstrates the fibrous connective tissue stroma separating the numerous papillary projections. They appear complex at low power. Blood and secretions are frequently identified. (Right) This portion of the temporal bone demonstrates a small papillary projection [B], an early development of an endolymphatic sac tumor. This was in a patient with von Hippel-Lindau. (Courtesy L. Michaels, MD.)

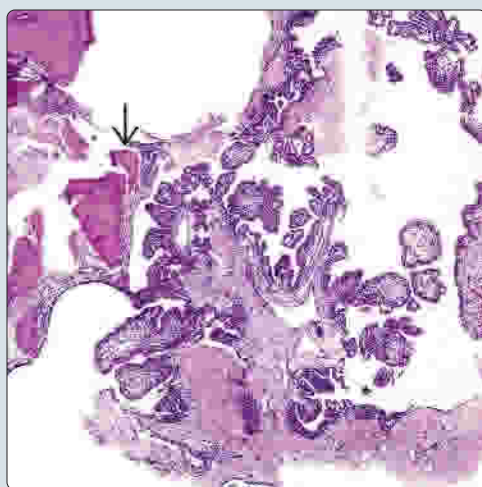


Microscopic Endolymphatic Sac Tumor (ELST) Within Bone



Broad Papillae With Bone Fragments

(Left) There is a fibrous connective tissue stroma and broad papillae in this field of an ELST. Bone fragments [B] are present in the background, although only remodeled rather than destroyed. (Right) The bland morphologic appearance and cuboidal-columnar pattern can sometimes mimic metastatic thyroid papillary carcinoma. Note the secretions creating a scalloping within the lumen [B].



Secretions Within Follicles



TERMINOLOGY

Abbreviations

- Endolymphatic sac tumor (ELST)

Synonyms

- Papillary neoplasm of endolymphatic sac
- Aggressive adenomatous tumor
- Papillary adenomatous tumors
- Heffner tumor

Definitions

- Papillary epithelial neoplasm arising within endolymphatic sac/duct, showing high association with von Hippel-Lindau (VHL) syndrome

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- *VHL* germline mutation
 - Autosomal dominant inheritance pattern
 - ~ 20% of cases reflect new mutations
 - *VHL* tumor suppressor gene (*VHL*)
 - Also called elongin binding protein and *G7* protein
 - *VHL* protein is involved in up-regulation of hypoxic response (via hypoxia inducible factor [HIF]-1 alpha)
 - Mutations: Prevent production of any functional *VHL* protein or result in change of structure of *VHL* protein
 - Also involved in tumor formation
 - Central nervous system, kidneys, pancreas, adrenal glands, epididymis, broad ligament, and endolymphatic sac
 - Microscopically, morphologically similar changes in adjacent epithelium
- Vast majority of cases develop in patients with VHL syndrome

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~ 1 in 35,000-40,000 people have VHL
 - Up to 16% have endolymphatic sac tumors (but rare event)
- Age
 - Mean: 30-40 years; wide range at presentation
- Sex
 - Equal gender distribution

Site

- Posterior petrous bone: Intraosseous vestibular aqueduct portion or operculum of endolymphatic duct/sac system
- Endolymphatic sac or endolymphatic duct, retrolabyrinthine

Presentation

- Symptoms usually present for years, suggesting slow tumor growth
- Progressive, ipsilateral hearing loss
 - Sensorineural >> conductive usually
 - Tinnitus
 - Annual audiometry for screening of VHL patients
- Vertigo, ataxia, vestibular dysfunction

- Facial nerve palsy
- May show stigmata of VHL in other anatomic sites: Kidney, pancreas, cerebellum

Treatment

- Surgical approaches
 - Wide excision with attempt at hearing preservation
 - CSF leak and nerve palsy potential complications
- Radiation
 - No role for radiation therapy

Prognosis

- Good, depending on extent of tumor (difficult to eradicate based on size and anatomic site)
 - Anatomic complexity may explain distinct difficulties in removal
- Dependent on other disease(s) present, such as hemangioblastoma, renal cell carcinoma, pancreatic cyst
- Recurrences develop if incompletely excised
- No metastatic potential

IMAGING

MR Findings

- T1-weighted images show hyperintensity (hypervascularity) of heterogeneous mass

CT Findings

- Lytic, multilocular lesion with bone destruction, centered on endolymphatic sac (between internal auditory canal and sigmoid sinus)
- Tumor may expand to involve cerebellopontine angle, cranial fossa, and middle ear

MACROSCOPIC

General Features

- Bilateral tumors are almost always associated with VHL
- Destruction of mastoid air spaces and extending into middle ear
- Frequently extends into posterior cranial fossa (cerebellum)

Size

- Depends on patient age: Larger lesions in older age patients
- Mean: 2 cm; range up to 10 cm

MICROSCOPIC

Histologic Features

- Unencapsulated, destructive lesions
- Bone invasion and remodeling
- Simple, coarse, broad papillary projections
- Cystic spaces often filled with fluid or extravasated erythrocytes
- Acinar-follicular spaces filled with inspissated material may simulate thyroid-like differentiation
- Single layer of low cuboidal to columnar epithelial cells
- Clear to slightly eosinophilic, granular cytoplasm with indistinct cell borders/membranes
- Small, round, hyperchromatic nuclei
- Fibrovascular cores within papillary structures

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CK-PAN	Positive	Cytoplasmic	Often weak
CK7	Positive	Cytoplasmic	
CK8/18/CAM5.2	Positive	Cytoplasmic	
EMA	Positive	Cell membrane & cytoplasm	Often weak
CK5/6	Positive	Cell membrane & cytoplasm	
S100	Positive	Nuclear & cytoplasmic	Often weak
Vimentin	Positive	Cytoplasmic	
NSE	Positive	Cytoplasmic	Weak and focal
GFAP	Positive	Cytoplasmic	Weak and focal
CD56	Positive	Cytoplasmic	Variably positive
TTF-1	Negative		
Thyroglobulin	Negative		

ANCILLARY TESTS

Immunohistochemistry

- Epithelial markers are usually **positive**

Genetic Testing

- Germline mutations of *VHL* tumor suppressor gene
 - 3p25-26 (short arm of chromosome 3) gene mutations
 - Between base pair 10,158,318 to base pair 10,168,761 on chromosome 3

DIFFERENTIAL DIAGNOSIS

Neuroendocrine Adenoma of Middle Ear

- a.k.a. middle ear adenoma (MEA)
- Middle ear affected by infiltrative, glandular neoplasm with biphasic appearance with delicate, salt and pepper nuclear features
- Positive:** Neuroendocrine and epithelial markers

Paraganglioma

- Nested, zellballen appearance, with isolated nuclear pleomorphism, and granular, coarse to salt and pepper nuclear chromatin distribution
- Positive:** Chromogranin and synaptophysin paraganglia cells; S100 protein sustentacular cells; **negative:** Epithelial markers

Choroid Plexus Papilloma

- Usually midline without temporal bone destruction
- EAAT-1 and Kir7.1 **positive** (not seen in ELST)

Metastatic Renal Cell Carcinoma (RCC)

- Not usually papillary
- Cytologic atypia is greater and extravasated erythrocytes more common in pseudoalveolar pattern
- Positive:** pax-2, CD10, and RCC

Metastatic Papillary Thyroid Carcinoma

- Nuclear contour irregularities, cleared nuclear chromatin, and nuclear overlapping

- Positive:** TTF-1, thyroglobulin

Middle Ear Adenocarcinoma

- Nuclear pleomorphism identified, but must exclude direct extension from adjacent organs

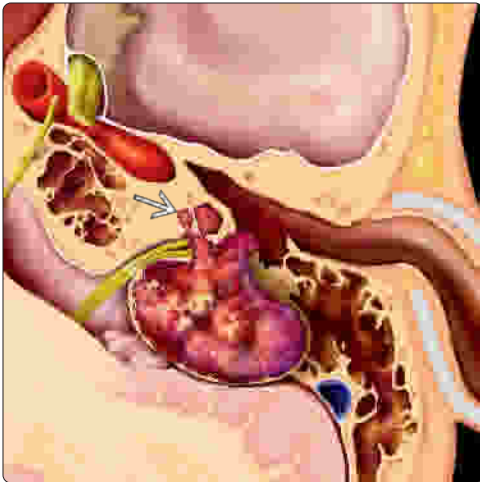
Ceruminous Adenoma

- External auditory canal tumor with biphasic appearance with inner cuboidal and outer basal cells
- Apocrine decapitation secretions and cerumen
- Biphasic immunoreactivity: Basal cells: p63, CK5/6, smooth muscle actin; luminal cells: CK7

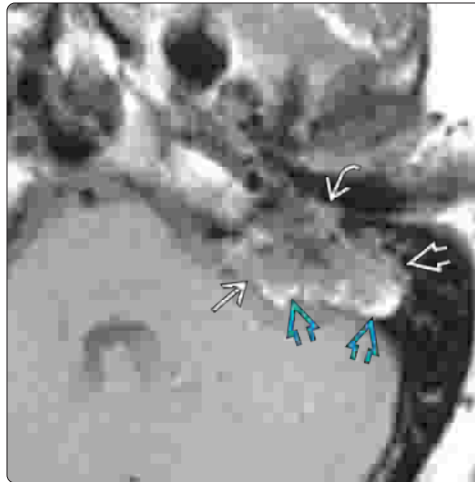
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Graphic of Anatomic Site

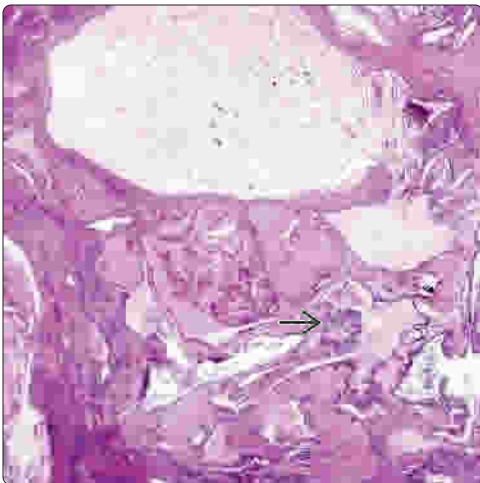


ELST on MR

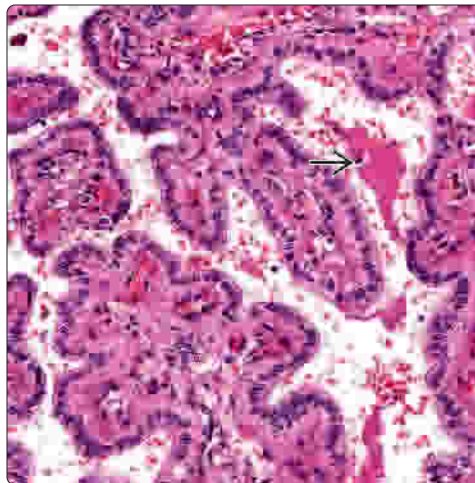


(Left) Axial graphic of the temporal bone shows the typical appearance of endolymphatic sac tumor. The tumor is vascular, shows a tendency to fistulize the inner ear, and contains bone fragments within the tumor matrix. (Right) Axial T1 unenhanced MR demonstrates an invasive tumor of the posterior wall of the left temporal bone that has reached the mastoid air cells and middle ear. The high signal (white) material represents methemoglobin within the tumor matrix.

Cholesterol Clefts in ELST



Coarse Papillae With Low Cuboidal Cells

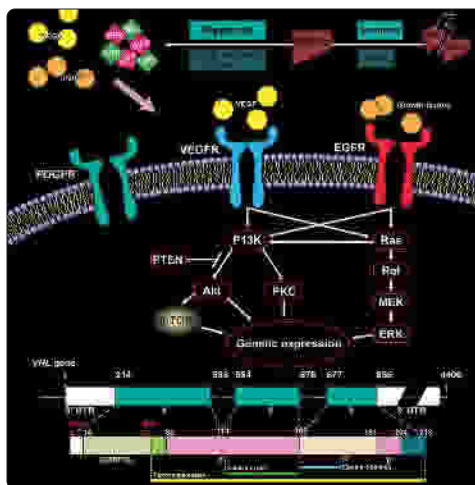


(Left) There are numerous cholesterol clefts in this ELST, which has undergone organization of hemorrhage. Papillary projections are still present along with secretions or concretions. (Right) High-power view shows cuboidal to low columnar cells lining the broad papillary projections. The nuclei are regular with coarse nuclear chromatin distribution. Inspissated material is seen.

CK7 Immunoreactivity



VHL Gene



(Left) The neoplastic cells are strongly and diffusely positive for a variety of epithelial immunohistochemistry markers. In this case the cells are stained with CK7, but keratin, CAM5.2, CK8/18, or EMA would also be positive in this tumor. (Right) Graphic demonstrates the very complex role the von Hippel-Lindau tumor suppressor gene, found on chromosome 3p25.3, plays in oxygen control. When the gene is mutated, other genes are transcribed, which results in the components of the disease complex.

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SECTION 8

Neck (Soft Tissue and Lymph Nodes)



Lymph Nodes	806
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Congenital/Genetic/Hereditary

Branchial Cleft Cyst	808
Cervical Thymic Cyst	814
Bronchogenic Cyst	816

Infectious

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Mycobacterial Spindle Cell Pseudotumor	824

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Sarcoidosis	826
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Reactive

Nodular Fasciitis	828
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Benign Neoplasm

Carotid Body Paraganglioma	830
Elastofibroma	836
Perineurioma	838
Lipoma	842
Spindle Cell Lipoma	844
Lipoblastoma	846
Nuchal-Type Fibroma	848
Hibernoma	850
Lymphangioma	852

Malignant Neoplasm

Metastatic Cystic Squamous Cell Carcinoma	854
Synovial Sarcoma	860
Chordoma	866
Liposarcoma	872

MACROSCOPIC ANATOMY

Lymph Nodes

- Round or reniform shape
- Normally < 1 cm in diameter
 - Larger during stimulation (2-3 cm in diameter)
- Tan-pink homogeneous cut surface
 - Nodular &/or white cut surface suspicious for malignancy
- Blood supply
 - Arteries and veins enter and exit at hilus, respectively
- Lymphatics
 - Afferent lymphatics enter in subcapsular sinus, lined by endothelium
 - Branching network of sinuses drains into efferent lymphatic vessels which exit at hilus

MICROSCOPIC ANATOMY

4 Compartments

- Cortical area, paracortex, medullary region, and sinuses

Cortical Areas

- **Primary follicle**
 - Homogeneous nodules of small darkly staining naive inactivated B lymphocytes
- **Secondary follicle**
 - Shows changes associated with antigenic stimulation (germinal center [GC], polarization, tingible body macrophages)
 - **GC:** Composed of centroblasts, centrocytes, small lymphocytes, tingible body macrophages, dendritic reticulum cells, small T cells
 - May undergo hyalinization (especially Castleman disease)
 - **Zonation:** Related to direction of antigen processing and process of B-cell maturation from centroblasts to centrocytes
 - Dark zone: Predominantly centroblasts oriented toward center of lymph node (LN)
 - Light zone: Predominantly centrocytes, oriented toward periphery

- Follicles may show infiltration by small lymphocytes
- Lack expression of Bcl-2

• Mantle zone

- Similar characteristics as primary follicle: Small dark staining tightly packed B cells surround GC
- Centrocytes with high affinity Ig survive and migrate to mantle zone with maturation continuing toward memory B cells and plasma cells

• Marginal zone

- Less compact B cells, more abundant cytoplasm, located along outer layer of mantle zone
- Mantle zone memory cells migrate to marginal zone

Paracortex

- Interfollicular area composed predominantly of T cells, with post capillary/high endothelial venules and interdigitating cells (IDC)
- T cells are mostly small and naive, may become activated and change into larger immunoblasts upon stimulation
- IDCs involved in antigen presentation, when present in large numbers, impart mottled appearance
- May become fibrotic (especially in inguinal LNs)

Medullary Region

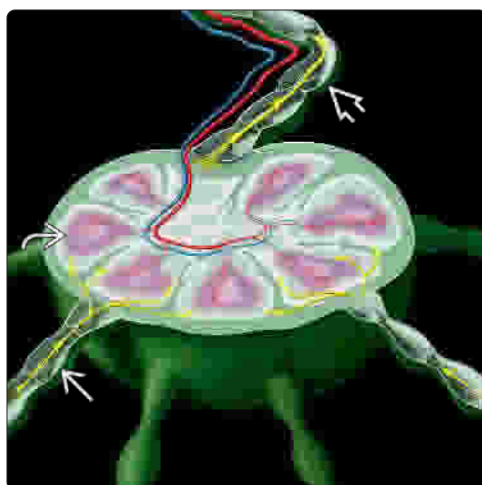
- Cords of cells: Lymphocytes, plasmacytoid lymphocytes, mature plasma cells, plasmablasts, and rare mast cells
- Site of plasma cell proliferation, differentiation, and antibody production
- Cords are separated by medullary sinuses

Sinuses

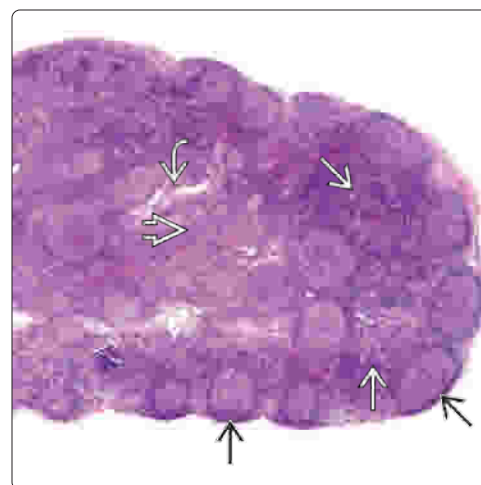
- Primarily in medullary region, but do extend up into cortex
- Subcapsular sinus located directly beneath capsule
- Carry lymph from afferent lymphatics through lymphoid parenchyma into efferent lymphatics located at LN hilum
- Lined by thin, pale-staining endothelial cells; acquire lining of macrophages within hilum
- Contain macrophages, lymphocytes, plasma cells, immunoblasts, and occasional neutrophils
- Thoracic/pulmonary lymph nodes show abundant anthracotic pigment and histiocytes

Graphic of Lymph Node Anatomy

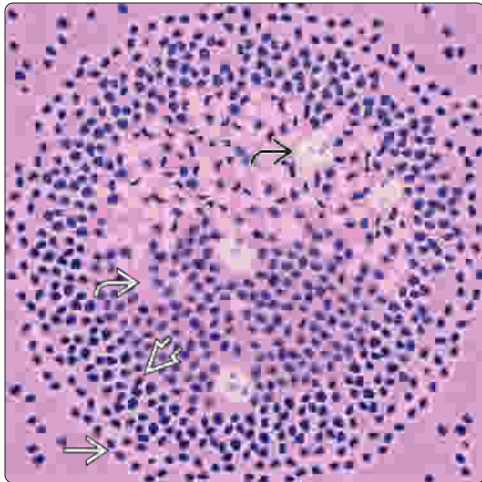
(Left) This lymph node (LN) graphic shows the usual arrangement of cortical-based follicles. The directional flow of lymph through afferent and efferent lymphatics is indicated by yellow arrows. (Right) Cortically based secondary follicles, paracortex, medullary region, and sinuses are visualized in this reactive-appearing lymph node (LN).



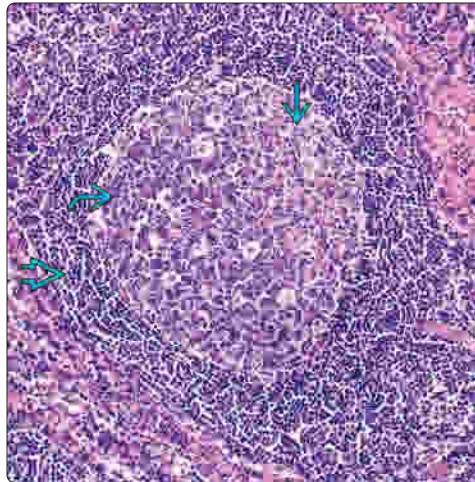
Lymph Node Histology



Graphic of Secondary Follicle

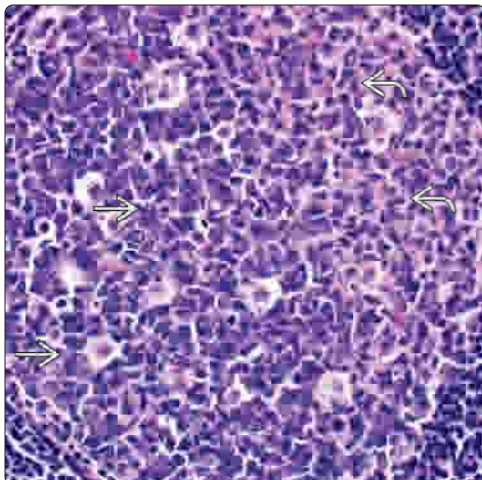


Histology of Secondary Follicle

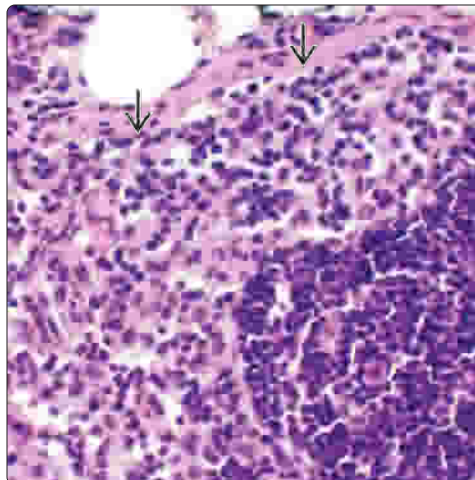


(Left) This illustration of a secondary follicle shows many of the key histologic features: Light and dark zonation, tingible body macrophages [X], follicular dendritic cells [X], mantle zone [X], and marginal zone [X]. (Right) A secondary follicle with dark and light zonation and a distinct surrounding mantle zone [X] is shown. The dark zone [X] consists predominantly of immature centroblasts and a few immunoblasts while the light zone [X] consists of more mature centrocytes. The surrounding mantle zone consists of naive B cells.

Histology of Germinal Center

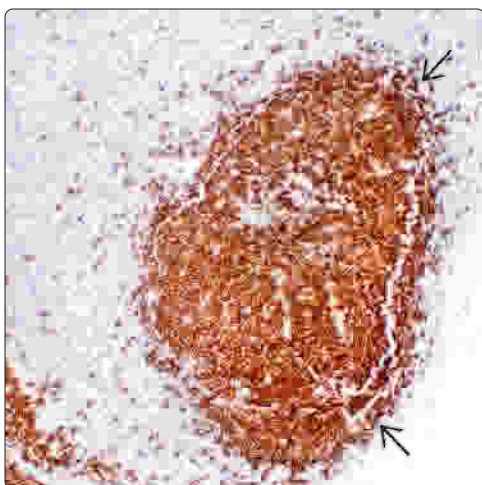


Lymph Node Subcapsular Sinus

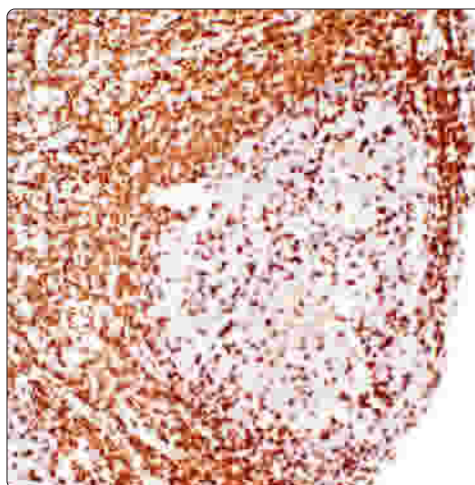


(Left) The predominance of centroblasts [X] in the dark zone and centrocytes [X] in the light zone of this germinal center is illustrated here at high power. (Right) A dilated subcapsular sinus [X] with numerous histiocytes (round nuclei, abundant eosinophilic cytoplasm) and scattered small lymphocytes is shown at medium power.

CD20 Immunostain of Follicle



CD3 Immunostain of Follicle



(Left) Medium-power view shows a cortical-based lymph node follicle [X] that is composed primarily of CD20(+) B cells. (Right) CD3 immunostain at medium power highlights the scattered T cells within the germinal center (follicular helper T cells) and the predominance of T cells within the paracortical region.

Branchial Cleft Cyst

KEY FACTS

TERMINOLOGY

- Branchial cleft cyst refers to congenital developmental lateral cervical cyst derived from remnants of 2nd branchial apparatus

ETIOLOGY/PATHOGENESIS

- Failure of obliteration of cervical sinus results in 2nd branchial cleft remnant (cyst, sinus, or fistula)

CLINICAL ISSUES

- BCC: ~ 20% of all congenital cervical cysts
- Bimodal presentation (< 5 years; 20-40 years)
- Waxing and waning, painless, compressible, cervical swelling
 - Enlarges after upper respiratory tract infection
- Along anterior border of sternocleidomastoid muscle
- Initial work-up of suspected branchial cleft anomaly (in order)

- Intravenous or oral antibiotics (if infected), FNA, endoscopy &/or radiographic studies, surgery
- Complete surgical excision yields low recurrence risk

MICROSCOPIC

- Cyst lined by various types of epithelium (90% stratified squamous)
 - Basement membrane often beneath epithelium
- Lymphoid aggregates in cyst wall
- Lumen is filled with keratinaceous debris in many cases

ANCILLARY TESTS

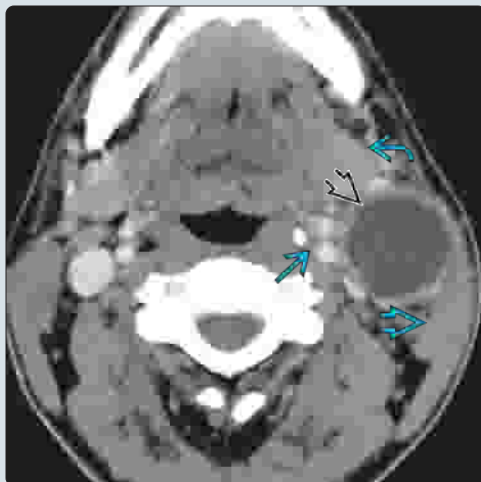
- p16 may show focal, strong staining of superficial squamous epithelium and interdigitating cells

TOP DIFFERENTIAL DIAGNOSES

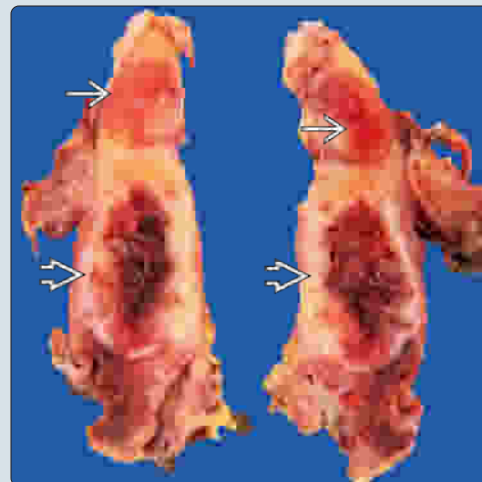
- Metastatic cystic squamous cell carcinoma, bronchiogenic cyst, cervical thymic cyst, metastatic cystic thyroid papillary carcinoma, thyroglossal duct cyst, dermoid cyst, laryngocele

CT of 2nd Branchial Cleft Cyst

(Left) Axial contrast-enhanced CT reveals a 2nd branchial cleft cyst located posterior to the submandibular gland, lateral to the carotid space, and anterior to the sternomastoid muscle. Capsule thickening suggests inflammation. (Right) The resection specimen includes a benign lymph node, separate from the cyst immediately below. Note the thick, fibrous connective tissue wall surrounding the cyst, filled with hemorrhagic and keratinaceous material.

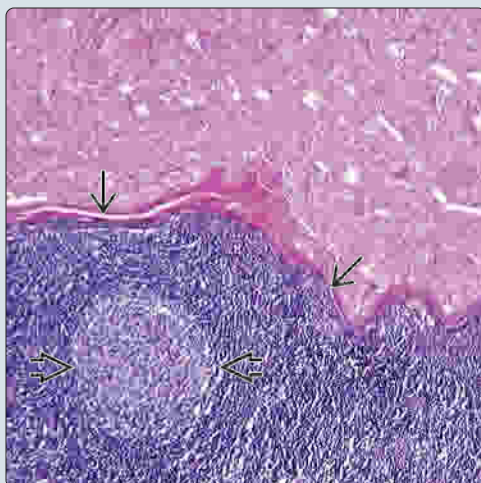


Gross Photo of Branchial Cleft Cyst

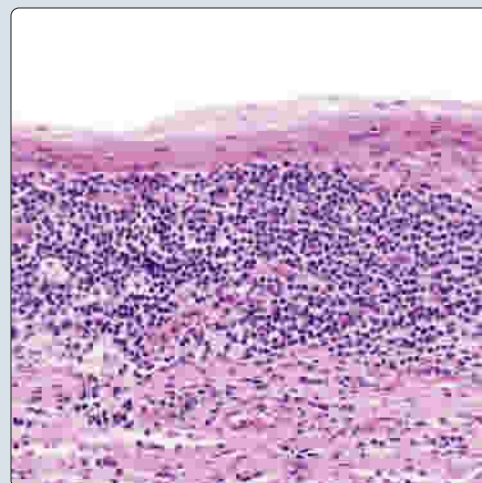


Keratinaceous Debris in Branchial Cleft Cyst

(Left) The lumen of this branchial cleft cyst (BCC) is filled with keratinaceous debris. There is a thin, squamous epithelium without any atypia. There is a germinal center within the associated lymphoid tissue. (Right) The cyst is lined by metaplastic squamous epithelium subtended by a very thin basement membrane between the epithelium and lymphoid tissue. Metaplasia is usually seen in patients who have had previous infection.



Metaplastic Squamous Lined Cyst



TERMINOLOGY

Abbreviations

- Branchial cleft cyst (BCC)

Synonyms

- Lateral neck cyst
- Cervical lymphoepithelial cyst

Definitions

- By convention, branchial cleft cyst refers to congenital developmental lateral cervical cyst derived from remnants of 2nd branchial apparatus
 - ~ 80-90% of all branchial anomalies arise from 2nd branchial apparatus
 - Encompasses branchial cyst, sinus, or fistula

ETIOLOGY/PATHOGENESIS

Branchial Apparatus

- Precursor of many head and neck structures
- 2nd branchial arch overgrows 2nd, 3rd, and 4th clefts, forming "cervical sinus"
- Embryogenesis usually complete by 6-7 weeks of gestation
- Failure of obliteration of cervical sinus results in 2nd branchial cleft remnant (cyst, sinus, or fistula)
 - Sinus is respiratory epithelium lined, but squamous metaplasia and lymphoid hyperplasia develop as consequence of immunologic stimulation during infection
- 2nd branchial cleft fistula extends from skin anterior to sternocleidomastoid muscle (SCM), through carotid artery bifurcation to terminate in tonsillar fossa
- 3rd and 4th branchial cleft cysts are very uncommon (< 5%)
 - Recurrent neck abscess or acute suppurative thyroiditis
 - Vast majority on left side (90-95%)
- Some authors posit cystic transformation of cervical lymph nodes (specifically in adults)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon
 - Still, BCC are 1 of most commonly encountered congenital anomalies in pediatric otolaryngic practice
 - Thyroglossal duct cysts are most common
 - BCC accounts for ~ 20% of all congenital cervical cysts
 - Cysts >> sinuses (3:1)
 - ~ 80-90% of all branchial cleft anomalies are 2nd branchial cleft cysts
 - 4th branchial cleft anomalies are rare and involve larynx (neonatal stridor and recurrent deep neck infection)
- Age
 - Bimodal presentation
 - < 5 years old (24%)
 - 20-40 years old (75%)
 - ~ 1% in > 50 years
- Sex
 - Equal gender distribution

Site

- Lateral neck near mandibular angle
- Along anterior border of SCM
 - Anywhere from hyoid bone to suprasternal notch
- Curiously, left-sided predominance for 4th branchial anomalies (> 90%)

Presentation

- Painless cervical swelling
 - Along anterior border of SCM
 - Often present for long duration
 - May be painful (if infected)
- Waxing and waning lesion
 - Frequently enlarges in concert with upper respiratory tract infection
 - Patients present during phase of recent enlargement
 - May lie dormant (clinically silent) for years
- Compressible, fluctuant
- Mucoid or pus-like secretions from sinus tract skin opening (when opening is present)
 - Patients present with external fistulae ± internal opening
- Clinically, some lesions may mimic parotid mass or odontogenic infection
- Bilateral lesions are usually identified in syndromic or familial association
- Clinically, 1st or 4th BCC more likely to have incision and drainage procedures, resulting in recurrence
- **Important:** Must consider metastatic cystic squamous cell carcinoma in adults

Endoscopic Findings

- Advocated as part of initial assessment of neck cyst
 - Assess internal opening or draining sinus/fistula

Natural History

- Repeated infections and inflammation

Treatment

- Options, risks, complications
 - Initial work-up of suspected branchial cleft anomaly (in order)
 - Intravenous or oral antibiotics (if infected)
 - Fine-needle aspiration
 - Endoscopy (concurrent with surgery in some cases)
 - Radiographic studies
 - Surgery in nonresolving cases
 - Avoid repeated incision and drainage, as it yields high recurrence rate
 - Noninfected lesions are more easily removed than infected lesions
 - Entire fistula tract must be removed to prevent recurrence
 - Complications include possible wound infection and cranial nerve paresis
- Surgical approaches
 - Combined simultaneous endoscopic identification of sinus tract with lateral external cervical dissection
 - Cauterization of fistula used by some practitioners
 - Endoscopic placement of catheter into sinus lumen before surgical exploration
 - Complete surgical excision

- May be difficult in recurrent cases due to scarring
- Excision performed during quiescent phase (no active infection; 6-8 weeks after antibiotics)
- May need to include thyroid lobectomy to decrease recurrences
- Must dissect around cyst bed to exclude fistula
 - If superomedial tract: Usually ends in faucial tonsil
 - If inferior tract: Travels down carotid space, exiting in supraclavicular area skin

Prognosis

- Lesions are benign without malignant potential
- Recurrence rate is variable
 - < 3% if not infected before surgery
 - ~ 20% if infected or previously incised/drained or incompletely removed

IMAGING

Radiographic Findings

- Combination of radiographic studies and endoscopy greatly improve surgical management and outcome
- Contrast CT (or MR) will easily suggest this diagnosis and differentiate it from solid mass
- Well-circumscribed nonenhancing low-density cystic mass with smooth cavity and thin wall (unless infected)
 - If infected, wall is thicker and enhances (cellulitis)
- Cystic, ovoid to rounded mucoid density mass in characteristic location is diagnostic
- Location
 - Posterolateral to submandibular gland
 - Lateral to carotid space
 - Anteromedial to sternocleidomastoid muscle
 - Most are at or immediately caudal to mandibular angle
- Focal rim of cyst extending to carotid bifurcation
 - Notch sign is pathognomonic for 2nd BCC

MACROSCOPIC

General Features

- Unilocular, containing clear to grumous material

Size

- Wide range, up to 10 cm

MICROSCOPIC

Histologic Features

- Usually unilocular cyst
- Cyst lined by various types of epithelium
 - Stratified squamous (90%)
 - Respiratory epithelium (~ 8%)
 - Considered native lining in uninflamed cyst
 - Transitions or both (2%)
- Lumen is filled with keratinaceous debris in many cases
- Lymphoid aggregates usually subtend epithelial lining
 - Basement membrane frequently seen between epithelium and lymphoid elements
- Reactive germinal centers commonly present (~ 80%)
- Lymph node architecture is not present
 - No subcapsular sinus, medullary region, or interfollicular zone

- Acute and chronic inflammation frequently present
- Foreign body giant cell reaction within wall of cyst
- Fibrosis is frequently seen
 - Not heavy, thick "capsule" formation seen in metastatic cystic SCC
- Salivary gland tissue may be detected in wall
- Adnexa and cartilage are not seen in this type of BCC
 - Only seen in 1st branchial cleft cysts/sinuses
- Absence of dysplasia, pleomorphism, increased mitoses, and carcinoma

ANCILLARY TESTS

Cytology

- Fine-needle aspiration is recommended in evaluation of all neck cysts
 - Usually of residual cyst post-antibiotic therapy
- Thick, yellow, pus-like material is aspirated
- Smears are generally cellular
- Comprised of anucleate squames and mature squamous epithelium
 - Columnar respiratory type cells are less common
- Amorphous debris often associated with macrophages
- Lymphoid infiltrate, including plasma cells
- Acute inflammatory cells if infected

Immunohistochemistry

- Variety of keratins are positive, depending on type of lining
 - Pseudostratified respiratory, transitional, stratified keratinizing, or nonkeratinizing squamous epithelium
- p16 negative in BCC while positive in metastatic SCC of oropharyngeal origin
- Isolated cells are strongly positive with p16, usually in epithelial cells surrounded by lymphocytes (interdigitating cells)
- p16 may show focal, strong staining of superficial squamous epithelium and interdigitating cells
- Glucose transporter 1 (*GLUT-1*) negative in BCC but positive in metastatic cystic SCC

DIFFERENTIAL DIAGNOSIS

Metastatic Cystic Squamous Cell Carcinoma

- Jugulodigastric lymph node most commonly affected
- Unilocular cyst
- Very thick and well-developed capsule
- Subcapsular sinus, medullary zone, and interfollicular zones usually identified
- Ribbon-like distribution of atypical epithelium
- Lack of maturation, cellular enlargement, mitoses
- Pleomorphism is often limited and subtle, although can be profound in some cases
- Primary usually identified in
 - Tonsil and base of tongue: Frequently p16 positive
 - Nasopharynx: Frequently EBER positive
- Primary branchiogenic carcinoma **does not** exist

Bronchogenic Cyst

- Identified in subcutaneous tissue of supraclavicular region
- Radiographic appearance is different from BCC: Low in neck
- Cyst is lined by respiratory mucosa

- Cyst wall containing smooth muscle and bronchial glands

Cervical Thymic Cyst

- Often develop in children
- Affecting lateral cervical region
 - Angle of mandible to sternum, although usually lower neck
- Thymic tissue is present in cyst wall
 - Hassall corpuscles (squamous eddies)
 - Calcifications
 - Lymphoid elements

Metastatic Cystic Thyroid Papillary Carcinoma

- Lymph node architecture is easily identified
- May be unilocular lesion, with only serum or clear fluid in lumen
- Lining shows characteristic features of thyroid papillary carcinoma
 - Large cuboidal to columnar cells
 - Cellular crowding and overlapping
 - Cells have high nuclear to cytoplasmic ratio
 - Nuclear features of papillary carcinoma
 - Nuclear grooves, nuclear contour irregularities, nuclear folds
 - Nuclear enlargement, oval and elongated nuclei with overlapping
 - Intranuclear cytoplasmic inclusions
 - Nuclear chromatin clearing with condensation along nuclear membranes
 - Papillary architecture is frequently absent
 - **Positive:** Thyroglobulin, TTF-1, pax-8

Lymphangioma

- Generally clinical consideration
- Usually involves posterior cervical space
- Endothelial-lined spaces with serum, lymphocytes, and smooth muscle wall

Thyroglossal Duct Cyst

- Midline location or just off midline
- Cyst lined by squamous or respiratory epithelium that is associated with thyroid tissue
 - Thyroid tissue is often quite limited in extent
- Hyoid bone involved

Dermoid Cyst

- Sequestration of ectodermal tissue only
- Floor of mouth is most common location
- Squamous lining without lymphoid elements
- **No** other components
 - Muscle, nerve, or cartilage

Laryngocele

- Midline lesion, seldom confused with BCC
- Clinically classified into internal, external, and mixed types
- Lacks lymphoid stroma

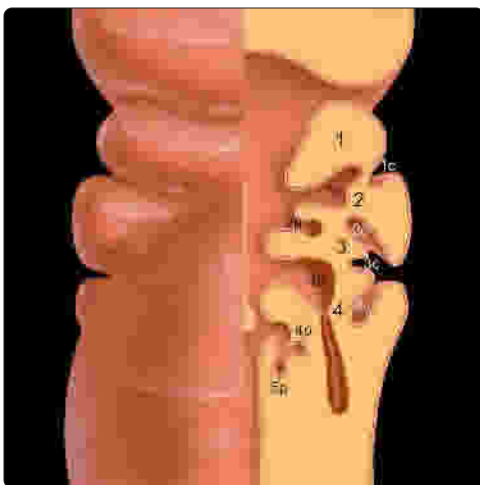
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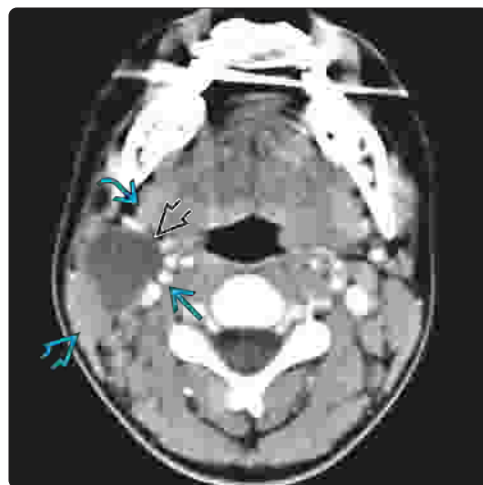
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Branchial Apparatus Development Graphic

(Left) The failure of a branchial apparatus cleft (c) or pouch (p) to involute or fuse during embryologic development results in the development of 2nd, 3rd, and 4th branchial cleft anomalies. (Right) CT shows a low-attenuation nonenhancing right branchial cleft cyst anterolateral to the carotid sheath, anteromedial to the sternocleidomastoid muscle (SCM), and posterolateral to the submandibular gland. This is characteristic of a noninflamed branchial cleft cyst.

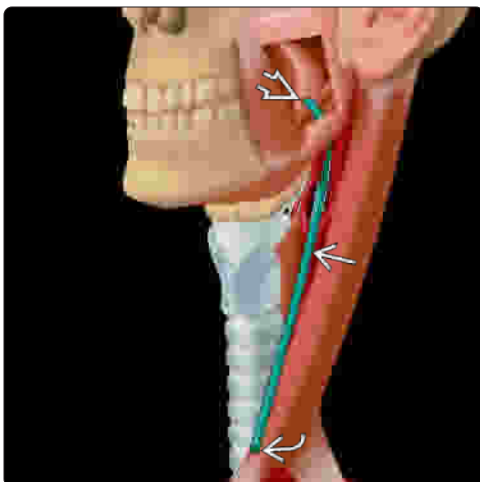


CT of Nonenhancing Branchial Cleft Cyst



Graphic of Branchial Apparatus Tract

(Left) A 2nd branchial cleft cyst/sinus/fistula can develop anywhere along the normal development of the branchial pouches and arches. The opening in the tonsil may be associated with a tract along the anterior border of the SCM, which extends to a supraclavicular skin opening. (Right) Plain film image from a lipiodol fistulogram demonstrates the presence of a complete fistulous tract extending from the tonsillar fossa in the oropharynx to the right supraclavicular fossa skin opening.

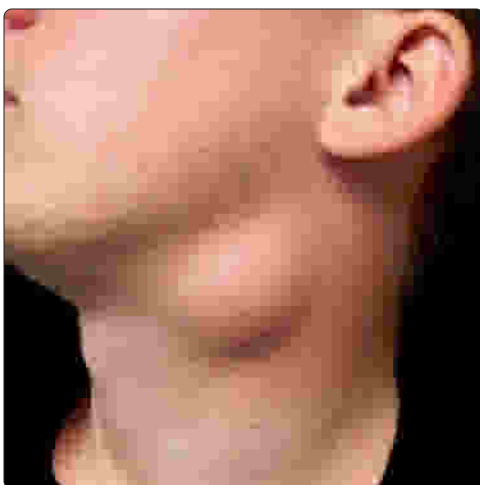


Fistulogram of Branchial Cleft Cyst Tract

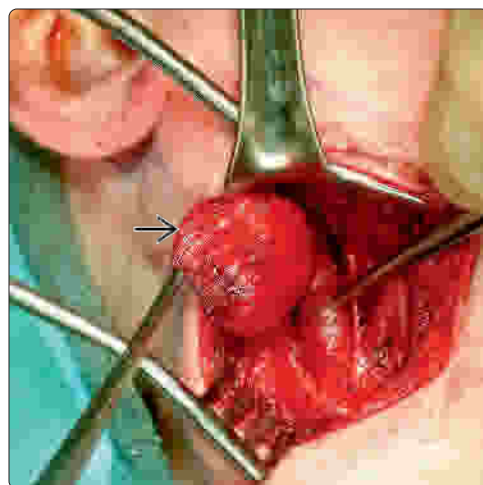


Mass in Lateral Neck of Young Man

(Left) This clinical photograph shows a compressible lateral neck mass in a young adult male, quite characteristic for a 2nd branchial cleft cyst. The patient came to clinical attention after an upper respiratory tract viral infection. (Right) The cyst has been retracted out of the operative field, highlighting the intimate association with the muscles, veins, arteries, and nerves of the neck.



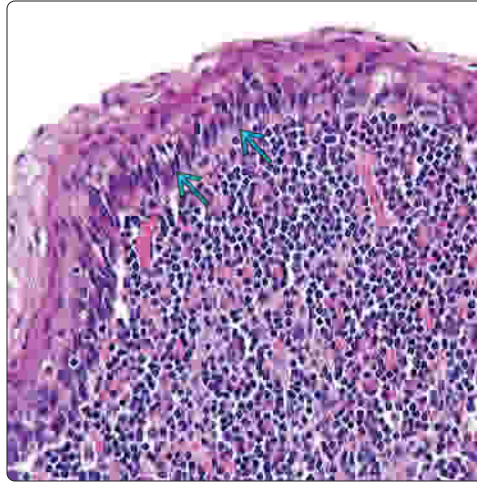
Intraoperative Photograph of Branchial Cleft Cyst



Unilocular Cyst With Mature Squamous Lining

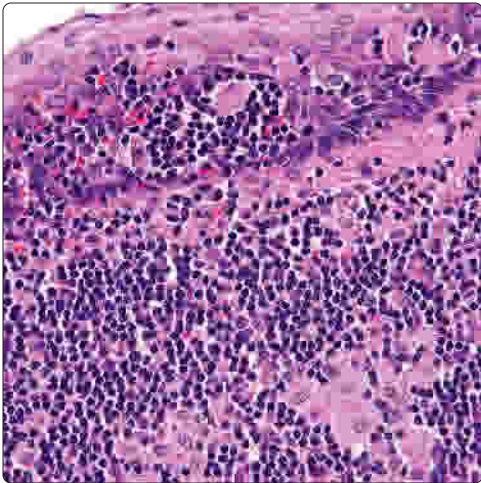


Cyst Lined by Metaplastic Squamous Cells

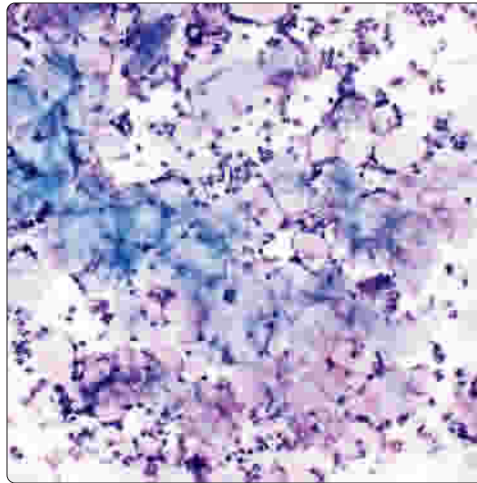


(Left) As seen here, there is a very thin, mature squamous epithelium lining the unilocular cyst. There is keratinaceous debris with cholesterol clefts. The stroma contains lymphoid elements. (Right) The cyst is lined by metaplastic squamous epithelium, although a residuum of columnar epithelium is still present. There is a very thin basement membrane between the epithelium and lymphoid tissue.

Mature Squamous Epithelium

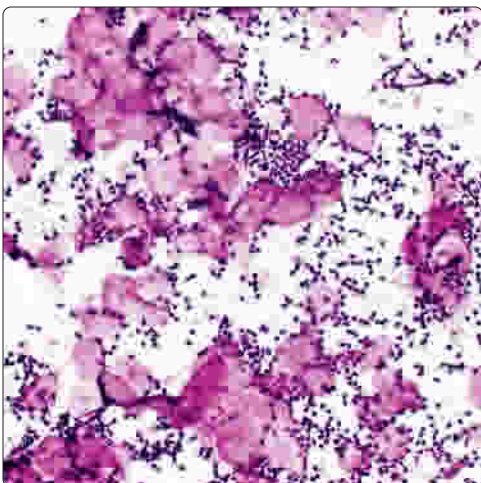


Anucleated Squames With Debris

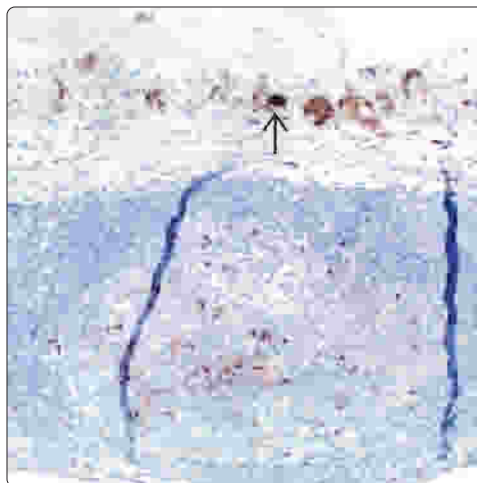


(Left) The squamous epithelium seen here is mature and lacks cytologic atypia. A well-developed basement membrane is seen, separating the epithelium from the stroma. Histiocytes are also present within the lymphoid background. (Right) Numerous acute inflammatory cells are seen in direct association with the anucleated squamous cells. Keratin debris like this is quite characteristic of a branchial cleft cyst. There is no cytologic atypia and no irregular cell shapes.

Neutrophils With Anucleated Squames



p16 Focal Reaction in Interdigitating Cells



(Left) There are many neutrophils intimately associated with squamous and anucleated squames in this smear from a BCC. There is no pleomorphism, no irregular shapes, and no mitotic figures. Necrosis is absent, although debris is present. (Right) Focal, strong positive reaction with p16 of selected epithelial cells within the cyst lining of a BCC. This type of limited reaction is common in inflamed or infected BCC.

Cervical Thymic Cyst

KEY FACTS

TERMINOLOGY

- Congenital cyst that develops within embryonic remnants of thymus

CLINICAL ISSUES

- Rare
- Male > Female
- Majority (67%) occur during 1st decade of life
- Most common in pediatric population
- Found anywhere between angle of mandible and sternum, including lateral and midline neck
 - Most common location anterior cervical triangle
- Majority of patients present with slow-growing, painless, unilateral neck mass
- Simple excision is curative

IMAGING

- Shows cystic nature of lesion

- Demonstrates association with large vessels (e.g., intimate relationship to carotid sheath)






MICROSCOPIC

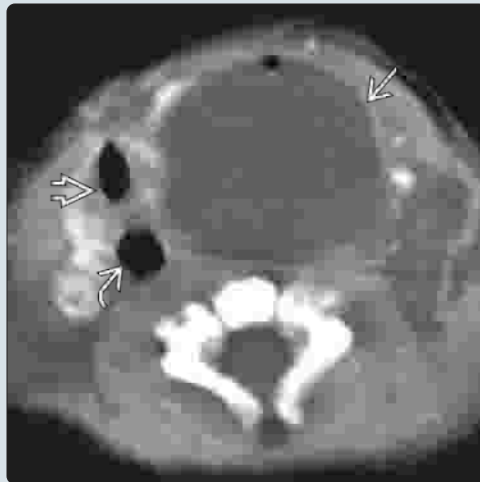
- Cystic lesion variably lined by cuboidal, columnar, &/or squamous epithelium
- By definition, wall contains thymic tissue including Hassall corpuscles
 - Concentric islands/aggregates of squamous cells often with central keratinization
- Foreign body giant cell reaction &/or cholesterol granulomas commonly seen

TOP DIFFERENTIAL DIAGNOSES

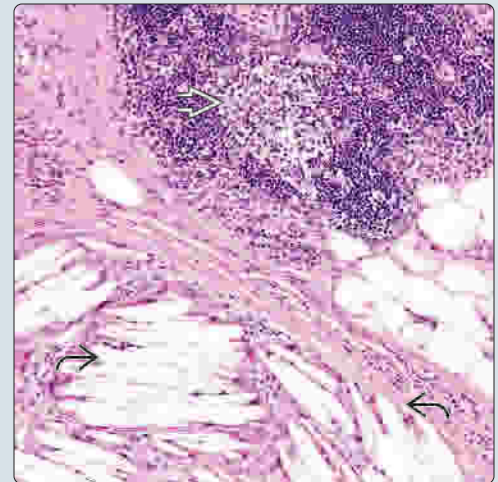
- Branchial cleft cyst
- Cystic hygroma (lymphangioma)
- Dermoid cyst
- Thyroglossal duct cyst

Thymic Cyst in Infant





(Left) Axial CECT in an infant with an infected thymic cyst demonstrates a small bubble of gas anteriorly, within a large left-sided cystic neck mass  that causes significant deviation of the airway  and esophagus  to the right. (From DI: H&N.) (Right) Hematoxylin and eosin shows the common finding of the presence of cholesterol granulomas in the cyst wall , which may also include lymphoid follicles, including germinal centers .

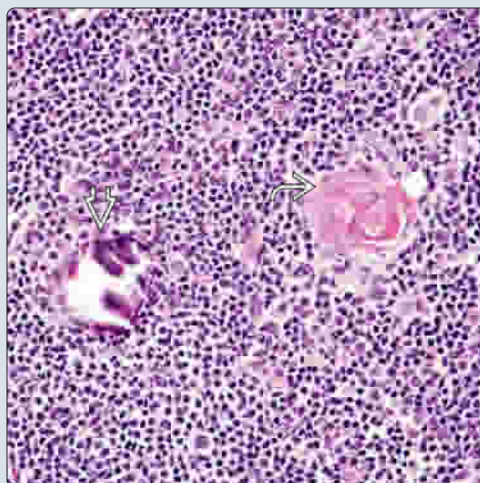


Cholesterol Granulomas

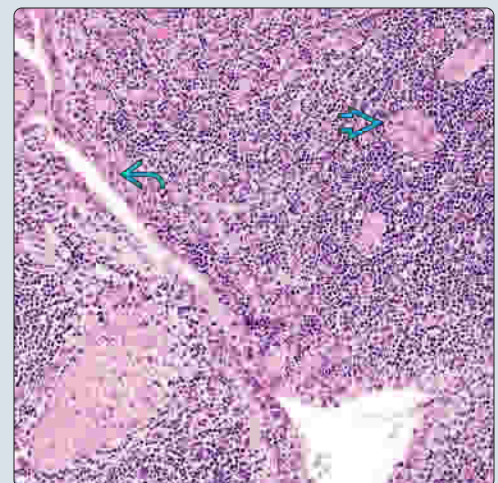


Hassall Corpuscle

(Left) The wall of the cyst includes an identifiable Hassall corpuscle  characterized by a concentric island of squamous cells with central keratinization; microcalcification  is focally present. Identification of thymic tissue may require extensive sampling. (Right) Medium-power hematoxylin and eosin shows an epithelial-lined cyst  with a dense mixed inflammatory cell infiltrate and a Hassall corpuscle . These findings in conjunction with a cyst wall are diagnostic of a thymic cyst.



Epithelial-Lined Cyst



TERMINOLOGY

Definitions

- Congenital cyst that develops within embryonic remnants of thymus

ETIOLOGY/PATHOGENESIS

Embryogenesis

- Thymus develops in 6th week of gestation, arising primarily from 3rd branchial pouch (mesoderm)
 - Failure of descent or failure to involute results in thymic abnormalities, including cervical thymic cyst

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare
- Age
 - Most common in pediatric population
 - Majority occur during 1st decade of life
 - Remainder occur in 2nd-3rd decades
 - Rarely occurs in older adults
- Sex
 - Male > female

Site

- Found anywhere between angle of mandible and sternum, including lateral and midline neck
 - Most common location is anterior cervical triangle
 - May extend into mediastinum or may be in continuity with intrathoracic thymus gland

Presentation

- Slow-growing, painless, unilateral neck mass
 - May transiently expand with Valsalva maneuver
- Uncommonly, presentation may include
 - Dyspnea, dysphagia, hoarseness, or pain
 - Vocal cord paralysis, stridor, odynophagia
 - Life-threatening airway obstruction
- Rarely (if ever) associated with sinus or fistula

Treatment

- Simple excision

Prognosis

- Cured following excision
 - No recurrences and no malignant transformation
 - No association with myasthenia gravis

IMAGING

CT Findings

- Identifies cyst, often intimately associated with vessels (carotid sheath)

MACROSCOPIC

General Features

- Unilocular or multilocular
- Cyst lining smooth or trabeculated; varying wall thickness

- Cystic content may include clear serous or hemorrhagic fluid, semi-solid debris

Size

- 1.4-17.0 cm

MICROSCOPIC

Histologic Features

- Cystic lesion variably lined by cuboidal, columnar, &/or squamous epithelium
 - When infected, lining epithelium may be replaced by fibrous tissue
- By definition, wall contains thymic tissue, including
 - Hassall corpuscles: Concentric islands/aggregates of squamous cells often with central keratinization
 - Lymphoid follicles
 - May require extensive sampling to document thymic tissue
- Foreign body giant cell reaction &/or cholesterol granulomas commonly seen
- Parathyroid parenchyma may be found in thymic cysts

DIFFERENTIAL DIAGNOSIS

Branchial Cleft Cyst (1st and 2nd Types)

- Tend to present at older age
- Lymphoid tissue in wall without thymic tissue
- Commonly associated with cysts and fistulas

Cystic Hygroma (Lymphangioma)

- Majority identified in lateral neck (posterior and anterior triangles)
- Endothelial cell-lined spaces containing proteinaceous fluid and lymphocytes
- Intervening stroma contains small amounts of fibrous connective tissue and smooth muscle with lymphoid aggregates
- Stroma may become inflamed and fibrotic following repeated infections

Dermoid Cyst

- Cyst wall contains cutaneous adnexal structures (hair follicles, sebaceous, eccrine, or apocrine glands)

Thyroglossal Duct Cyst

- Usually midline neck above thyroid isthmus but below level of hyoid bone
 - Nearly always connected to hyoid bone
 - Uncommonly may occur lateral to midline but does not occur in lateral portion of neck (i.e., lateral to jugular vein)
- Usually has thyroid follicular epithelium in wall

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4. Petropoulos I et al: Thymic cyst in the differential diagnosis of paediatric cervical masses. *B-ENT.* 2(1):35-7, 2006

Bronchogenic Cyst

KEY FACTS

TERMINOLOGY

- Rare congenital malformation of ventral foregut

CLINICAL ISSUES

- Pediatric population; rare in adults
- Midline superficial presternal or suprasternal is most common neck location
 - Less commonly: Lateral, thyroid, or subcutaneous
- Male > female (4:1)
- Presents with airway compression, dysphagia, infection, or may be asymptomatic
- Complete surgical excision is treatment of choice
- Excellent long-term clinical prognosis

IMAGING

- Best study: Contrast-enhanced MR T1WI or T2WI to show well-defined, solitary, smooth-bordered mass

MACROSCOPIC

- Grossly tubular, altered by infection
- Cut sections show clear serous to mucoid material

MICROSCOPIC

- Cyst lined by respiratory-type epithelium
- Cyst wall with mucoserous glands, hyaline cartilage, and smooth muscle

TOP DIFFERENTIAL DIAGNOSES

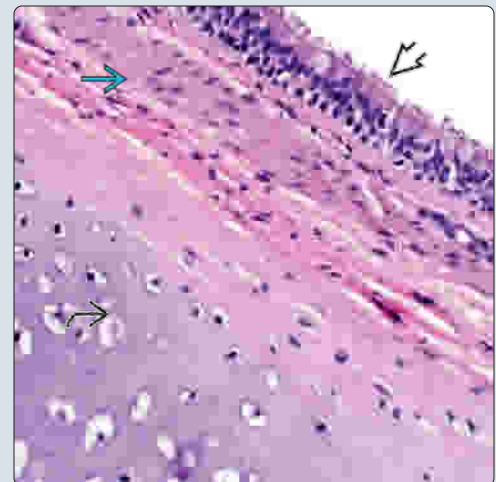
- Teratoma
- Dermoid cyst
- Branchial cleft cyst
- Thyroglossal duct cyst
- Cystic hygroma (lymphangioma)

Cyst Wall With Cartilage and Glands

(Left) This hematoxylin and eosin shows all the major features of a bronchogenic cyst: A cyst space lined by respiratory-type epithelium with a fibrous connective tissue wall that contains mucoserous glands, hyaline cartilage and smooth muscle. Multiple step sections may be needed to identify the different components. (Right) High-power image shows ciliated respiratory-type epithelium overlying a band of smooth muscle closely associated with cartilage.

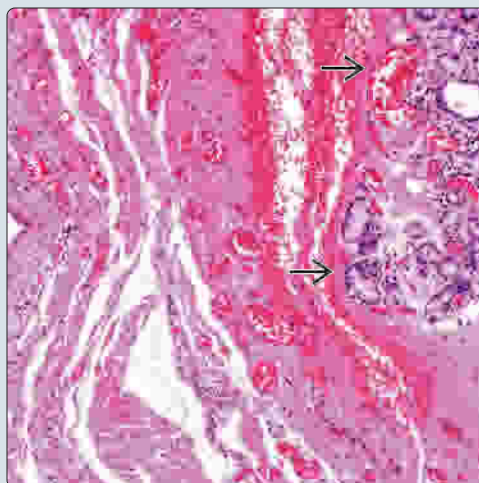


Ciliated Respiratory Epithelium

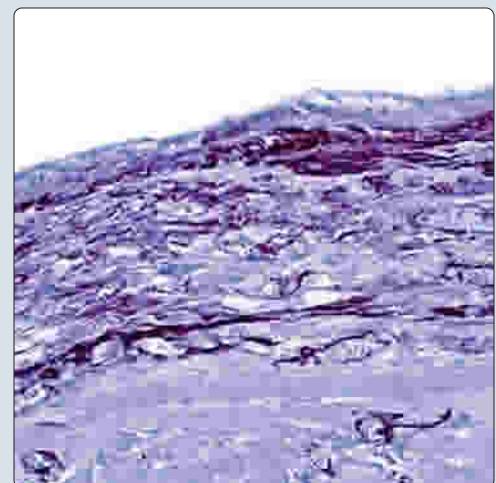


Wall Contents

(Left) Hematoxylin and eosin shows the fibrous wall of a bronchogenic cyst. Seromucinous glands are found throughout the wall and may contribute to the mucoid material found within the cyst. (Right) Smooth muscle, highlighted with smooth muscle actin, is characteristic within the wall of a bronchogenic cyst. Other cysts in the differential diagnosis, such as branchial cleft cysts and thyroglossal duct cysts, lack smooth muscle.



Highlighting of Smooth Muscle



TERMINOLOGY

Synonyms

- Bronchial cyst

Definitions

- Rare congenital malformation of ventral foregut
 - Enteric cyst, neurenteric cysts are part of same family

ETIOLOGY/PATHOGENESIS

Embryogenesis

- Derived from small buds of diverticula that separate from foregut during formation of tracheobronchial tree
- Usually between 26th-40th day of gestation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare
- Age
 - Pediatric population; rare in adults
- Sex
 - Male > female (4:1)

Site

- **Cervical**
 - Midline superficial presternal or suprasternal is most common location
 - Less commonly: Lateral, thyroid or subcutaneous
- **Noncervical**
 - Mediastinum
 - Around hilum

Presentation

- Compression of airway: Respiratory distress, cough, dyspnea
- Dysphagia
- Infection may be uncommon
 - Drainage associated with sinus tract
 - Fever
- Asymptomatic presentation is uncommon

Endoscopic Findings

- May show compression of laryngotracheal axis

Treatment

- Options, risks, complications
 - Drainage and infection are possible complications
- Surgical approaches
 - Complete surgical excision is treatment of choice
 - Neck exploration and selective dissection via transcervical approach
 - Great vessels and recurrent laryngeal nerve are at risk
 - If sinus tract is present, it should be removed with cyst
 - Drainage and ablation
 - Indicated for only high-risk adults

Prognosis

- Excellent long-term clinical prognosis
- Recurrence develops if incompletely excised
- Rare cases of carcinoma arising from bronchogenic cyst

IMAGING

Radiographic Findings

- Best study: Contrast-enhanced T1WI or T2WI MR to show homogeneously increased signal
- Well-defined, solitary, smooth-bordered mass

MACROSCOPIC

General Features

- Grossly tubular, altered by infection
- Cut sections show clear serous to mucoid material

MICROSCOPIC

Histologic Features

- Cyst lined by respiratory-type epithelium
 - Ciliated
 - Pseudostratified
 - Columnar
 - Epithelium may be altered by infection: Stratified squamous
- Cyst wall contains
 - Mucoserous glands
 - Hyaline cartilage
 - Haphazard smooth muscle
 - Scant lymphoid tissue

ANCILLARY TESTS

Cytology

- Normal ciliated columnar cells
- Serous or mucinous material

DIFFERENTIAL DIAGNOSIS

Teratoma

- Tissues from sites other than respiratory tract

Dermoid Cyst

- Hair and skin appendages
- Squamous epithelium

Branchial Cleft Cyst

- Lymphoid tissue arranged in germinal centers
- Typically has stratified squamous epithelium
- Lacks smooth muscle and cartilage
- Clinically, usually found laterally

Thyroglossal Duct Cyst

- Usually has thyroid follicles
- Lacks smooth muscle and cartilage

Cystic Hygroma (Lymphangioma)

- Variably sized lymphatic vessels

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2. Crespo Del Hierro J et al: Cervical bronchogenic cysts. *Acta Otorrinolaringol Esp*. 64(5):379-81, 2013
3. Moz U et al: Bronchogenic cysts of the neck: a rare localization and review of the literature. *Acta Otorhinolaryngol Ital*. 29(1):36-40, 2009
4. Newkirk KA et al: Bronchogenic cysts of the neck in adults. *Ann Otol Rhinol Laryngol*. 113(9):691-5, 2004

KEY FACTS

TERMINOLOGY

- Benign infectious disease caused by *Bartonella* organism introduced into humans via scratch or bite from cat, resulting in necrotizing granulomatous lymphadenitis

CLINICAL ISSUES

- Uncommon, but CSD is most common clinical disease associated with *Bartonella* infections
- Wide age range, but generally children/young adults
- Lymph node enlargement: Cervical ~ axillary > epitrochlear > supraclavicular ~ submandibular
- Scratch, bite, or papule at site of initial injury/inoculation (3-10 days), pustular or crusted with time
- Tender, painful, and swollen proximal regional lymph nodes with overlying erythematous skin
- Full resolution without treatment for most patients (< 1 month)

IMAGING

- CT: Matted lymph nodes with well-defined, thick, enhancing walls and low-attenuation centers (suppuration)

MICROSCOPIC

- Initial: Focal areas of necrosis with neutrophils; subcapsular sinuses packed with monocytoid B cells
- Intermediate: Debris and neutrophils fill central necrotic areas (microabscesses)
- Final: Lymphocytes blend with epithelioid histiocytes, multinucleated foreign body-type giant cells

ANCILLARY TESTS

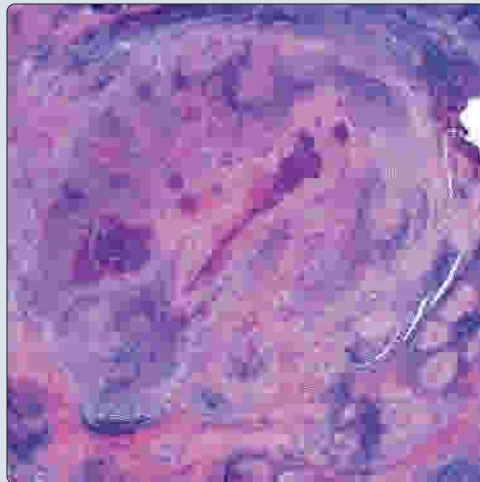
- Warthin-Starry stain highlights rare intracellular, 1-3 μ m rods, cocci or L-shaped polymorphic organisms

TOP DIFFERENTIAL DIAGNOSES

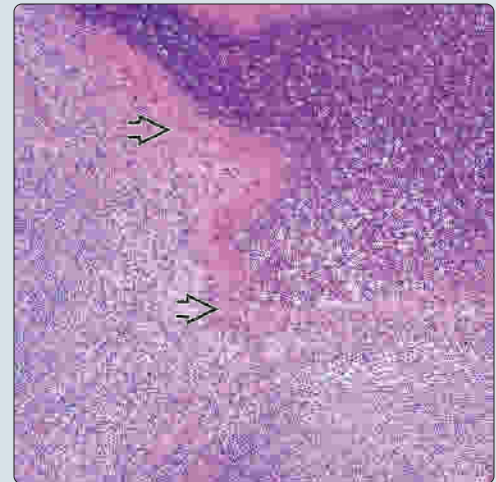
- Suppurative or nonsuppurative granulomatous inflammation, metastatic disease, branchial cleft cyst, sarcoid, Kikuchi-Fujimoto disease, Kawasaki disease

Stellate Caseating Granulomas

(Left) Low-power micrograph demonstrates stellate areas of central necrosis within this lymph node. The necrotic material is granular and blue, surrounded by histiocytes. (Right) The stellate abscesses are formed by debris and neutrophils filling in central areas within the lymph node. There is a palisade of histiocytes at the border with the surrounding parenchyma.

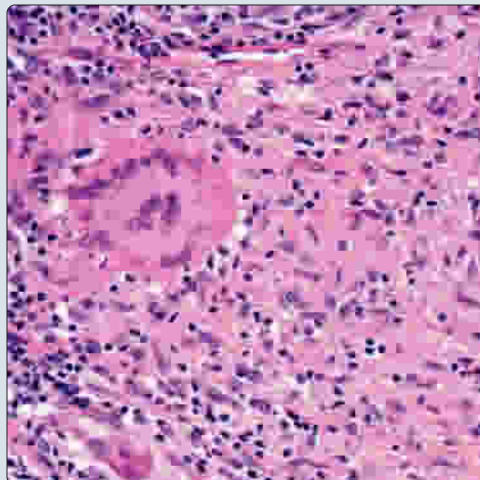


Palisading Histiocytes Around Debris

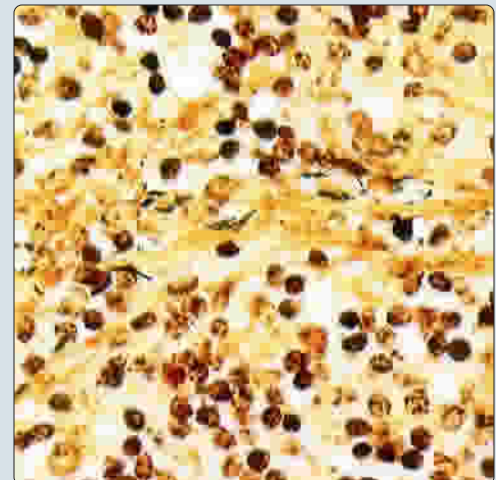


Multinucleated Giant Cells

(Left) A multinucleated foreign body-type giant cell is seen immediately adjacent to epithelioid histiocytes in this example of CSD. Again, isolated elements alone are nondiagnostic of CSD. (Right) There are multiple pleomorphic rod-shaped bacteria in this oil immersion photomicrograph stained with Warthin-Starry stain. The organisms are usually intracellular, 1-3 μ m rods, cocci or L-shaped bacteria. They are usually not this abundant, requiring careful oil examination to identify them.



Warthin-Starry Stains of Pleomorphic Rods



TERMINOLOGY

Abbreviations

- Cat scratch disease (CSD)

Synonyms

- Cat scratch fever
- Cat scratch adenitis
- Debre or Foshay-Mollaret syndrome

Definitions

- Benign infectious disease caused by *Bartonella* organism introduced into humans via scratch or bite from cat, resulting in necrotizing granulomatous lymphadenitis

ETIOLOGY/PATHOGENESIS

Transmission

- Causative organism is *Bartonella henselae* bacillus, a gram-negative pleomorphic rod-shaped bacteria
 - Organism originally classified as *Afipia felis*
- Asymptomatic, bacteremic cats with *Bartonella henselae* in their saliva serve as vectors by biting and scratching, causing skin erythema within 3-10 days
 - Kittens transmit disease more frequently than adult cats due to higher bacteremia
 - Cat fleas or ticks may serve as vector for cat-cat transmission or via feces-wound contact in humans
- Acute regional lymphadenopathy proximal to inoculation site developing after 1-3 weeks
- Most cases show gradual involution (self-limited) in 3-4 months

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon, but CSD is most common clinical disease associated with *Bartonella* infections
 - ~ 10-12% of patients with cervical lymphadenopathy
 - Most cases develop in fall and winter
- Age
 - Wide range, but generally children/young adults
- Sex
 - Equal gender distribution

Site

- Lymph node enlargement: Cervical ~ axillary > epitrochlear > supraclavicular ~ submandibular

Presentation

- Skin inoculation site &/or regional lymphadenitis most common
- Separated into classical and atypical presentations
 - **Classic:** Immunocompetent patients
 - Scratch, bite, or papule at site of initial injury/inoculation (3-10 days), pustular or crusted with time
 - 7-60 days for additional symptoms to develop
 - Tender, painful, and swollen proximal regional lymph nodes with overlying erythematous skin
 - Matted nodes may suppurate (10-15% of patients)

- Some patients may have concurrent fever, chills, malaise, headache, backache, arthralgia, abdominal pain
- Resolves spontaneously in about 30-120 days
- **Atypical (~ 10%):** Ocular, neurologic, &/or visceral organ involvement
 - Granulomatous conjunctivitis (Parinaud oculoglandular syndrome)
 - Optic neuritis, involvement of retina, and neuropathy
 - Immunocompromised patients may develop life-threatening systemic disease with severe complications
 - Enlarged spleen (abscess), swollen parotid gland (granuloma), liver enlargement (granuloma)
 - Neck stiffness, sore throat, respiratory distress, and trismus if abscess develops
 - Rare development of erythema nodosum (2% of patients)
 - Lymphadenitis may persist for years
- Must be considered in any fever of unknown origin; any lymphadenopathy syndromes

Laboratory Tests

- Serology for IgG antibody to *B. henselae* (titer > 1:256)
- Polymerase chain reaction (PCR) assay for organism (specialty laboratories)
- Culture is difficult to perform as organism is fastidious and slow-growing
- Elevated WBC: Mild neutrophilia/eosinophilia and elevated ESR

Treatment

- Options, risks, complications
 - Full resolution without treatment for most patients (< 1 month)
 - Excision, drainage, and antibiotic therapy
- Drugs
 - Wide variety of antibiotics are employed; azithromycin usually most frequently
 - However, antibiotics do not significantly affect cure rate or time to achieve cure

Prognosis

- Prognosis is generally excellent: Benign and self-limited
 - Rarely, persistent lymphadenopathy for months

IMAGING

Radiographic Findings

- CT is first-line tool for neck adenopathy evaluation
- Matted lymph nodes with well-defined, thick, enhancing walls and low-attenuation centers (suppuration) with surrounding cellulitis

MACROSCOPIC

General Features

- Confluent or matted lymph nodes with central pus/abscess

Size

- Range: Up to 10 cm

MICROSCOPIC**Histologic Features**

- Lymph node biopsy performed due to failure of other methods to diagnose disease and slow resolution
- Lymph node changes vary according to disease stage
 - Follicular hyperplasia (early stage)
 - Focal areas of necrosis with neutrophils; subcapsular sinuses packed with monocytoid B cells
 - Central stellate necrosis (middle stage)
 - Debris and neutrophils fill central necrotic areas (microabscesses), fibrin easily identified
 - Palisading epithelioid histiocytes create granulomas (late stage)
 - Lymphocytes blend with epithelioid histiocytes, multinucleated foreign body-type giant cells
 - Granuloma may be scattered throughout lymph node
 - Plasmacytoid dendritic cells are increased

ANCILLARY TESTS**Cytology**

- FNA used to diagnose granulomatous inflammation and to obtain culture material
- Necrotic debris in background, epithelioid histiocytes, possible palisading, giant cells

Histochemistry

- Warthin-Starry stain highlights focal and scant organisms
 - Intracellular, 1-3 µm rods, cocci or L-shaped bacteria
 - Difficult to interpret: High background in necrotic debris & macrophages
- **Weak reaction:** Red with Brown-Hopps tissue Gram stain; **negative:** Ziehl-Neelsen

Immunohistochemistry

- **Positive:** Monoclonal antibody to *B. henselae* (sensitive and specific, but fastidious)

PCR

- PCR of *B. henselae* or *quintana* is both sensitive and specific

DIFFERENTIAL DIAGNOSIS**Suppurative Granulomatous Inflammation**

- Mycobacterial infections (*Mycobacteria tuberculosis*, *M. avium-intracellulare*, *M. scrofulaceum*): Caseating but not stellate; many giant cells; positive with acid-fast stains
- Fungal infections: Necrotizing granulomas, but not usually stellate; fungi identified by special stains
- Staphylococcal and streptococcal infections: Begin as pharyngitis, dental caries, or osteomyelitis, then expand to cervical lymph nodes
- Tularemia (*Francisella tularensis*): Lymph node enlargement with possible necrotizing granulomas
- Yersinia: Lacks monocytoid B cells in suppurative lymphadenitis, usually affecting mesenteric lymph nodes
- Brucellosis (*Brucella* species): Human disease after exposure to contaminated dairy products; noncaseating granulomas; gram-negative coccobacilli
- Leishmaniasis (*Leishmania donovani*): Protozoan infection; obligate intracellular organisms identified by Giemsa

Nonsuppurative Granulomatous Inflammation

- Tuberculosis and BCG-histiocytosis: May be non-suppurative with giant cells and positive acid-fast stains
- Toxoplasmosis (*Toxoplasma gondii*): Cat vector; protozoan infection; may have granulomas, but not organized; lack necrosis, neutrophils and eosinophils

Metastatic Disease

- Painless, hard lymph nodes without skin erythema
- Metastatic squamous cell carcinoma, nasopharyngeal carcinoma, and thyroid carcinoma may have necrosis and granuloma
- Lymphoma, including Hodgkin lymphoma, may show extensive necrosis
- Pancytokeratin positive epithelial cells; specific lymphoid markers for lymphoma

Branchial Cleft Cyst

- Usually single, unilateral cystic mass lined by squamous epithelium without suppurative necrosis

Sarcoid

- Serologic and clinical evaluation is different
- Tight, well-formed, small granulomas, usually without necrosis
- Frequently have asteroid bodies or Schaumann bodies
- Infectious disease work-up (culture, special studies) negative

Kikuchi-Fujimoto Disease

- Histiocytic necrotizing lymphadenitis: Localized lymphadenopathy
- Well-defined, paracortical zones of necrosis with karyorrhectic debris
- No acute inflammatory cells (**absent** neutrophils)
- Granulomatous inflammation is present (palisading epithelioid histiocytes), with large, activated lymphocytes

Kawasaki Disease

- Acute, nonsuppurative lymphadenopathy, with effaced architecture and expanded interfollicular zones, lacking granuloma
- Zones of necrosis, often becoming confluent; nuclear debris and microthrombi of vessels

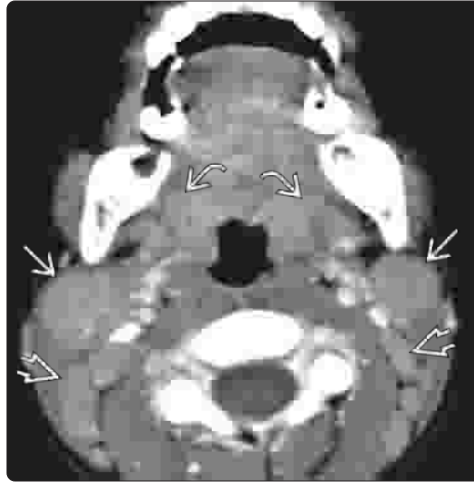
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Clinical Photograph of Lymphadenopathy

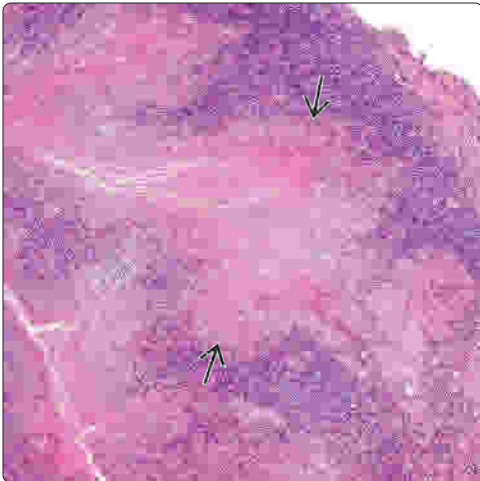


Bilateral Neck Lymphadenopathy on CT

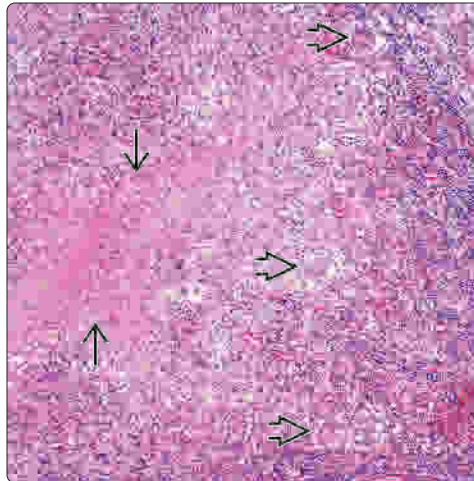


(Left) This man had been bitten on the arm by a feral cat about 3 weeks earlier. There is significant enlargement of the left preauricular/parotid gland region, with shiny, erythematous, warm skin covering the mass. (Right) Contrast-enhanced CT shows bilateral jugulodigastric, spinal accessory lymphadenopathy, and tonsillar hypertrophy in a patient who was bitten on her tongue by a cat. Imaging findings are not specific for CSD. (Courtesy R. Harnsberger, MD.)

Stellate Caseating Granuloma

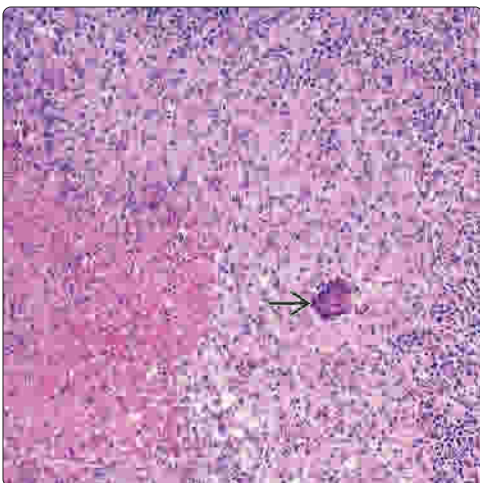


Foreign Body-Type Giant Cells

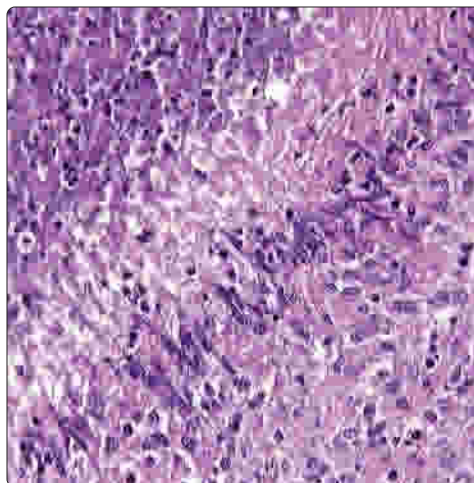


(Left) There is a background of follicular hyperplasia with stellate abscess formation within the lymph node. The brightly eosinophilic necrotic areas are surrounded by a palisade of epithelioid histiocytes and monocytoic cells. (Right) Necrotic material is surrounded by a well-developed layer of histiocytes. A number of foreign body-type giant cells are seen at the interface with the remaining lymphoid parenchyma. These features, while characteristic of CSD, are not specific.

Caseating Granulomatous Inflammation



Epithelioid Histiocytes



(Left) There is a palisade of epithelioid histiocytes surrounding an area of central caseation in this example of cat scratch disease. A giant cell is present along with other inflammatory elements. (Right) The histiocytes surrounding the area of caseating necrosis are epithelioid histiocytes, frequently showing elongation or footprint shape. These changes are nonspecific, requiring additional studies or clinical information to confirm the diagnosis.

KEY FACTS

TERMINOLOGY

- Pseudoneoplastic capillary proliferative lesion that occurs as complication of HIV infection and usually presents as cutaneous vascular lesion and is caused by opportunistic bacterial infection belonging to *Rochalimaea* species (*Rochalimaea henselae*) as well as by *Bartonella quintana*

ETIOLOGY/PATHOGENESIS

- Occurs most often in immunocompromised patients but may occur in patients with intact immune system
- May occur in association with Kaposi sarcoma and in solid organ transplant recipients (adults and pediatric patients)

CLINICAL ISSUES

- Full-dose erythromycin is 1st drug of choice
- Most commonly presents as cutaneous or mucocutaneous lesion
 - May involve other organs sites, including lymph nodes, spleen, liver as well as mucosal sites of upper respiratory tract and conjunctiva

- Commonly associated with systemic symptoms, including fever, chills, weight loss, and night sweats
- Full dose erythromycin is effective, often resulting in resolution of lesions

MICROSCOPIC

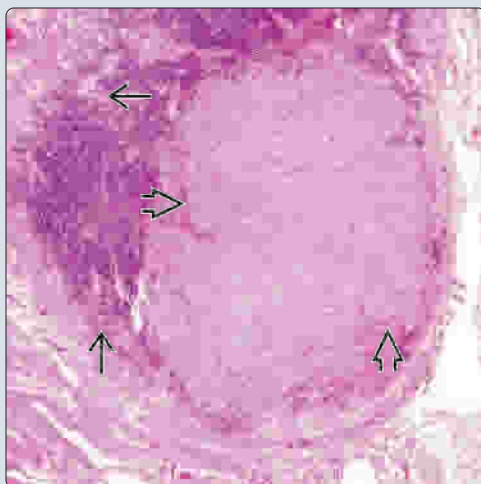
- Well-circumscribed lobular capillary proliferation
- Small capillaries arranged around ectatic vessels lined by prominent endothelial cells
 - Endothelial cells appear hyperchromatic and pleomorphic
 - Solid areas may be present and may obscure vascular proliferation
- Presence of neutrophils and neutrophilic debris adjacent to capillary proliferation with granular clumps that contain masses of bacilli

ANCILLARY TESTS

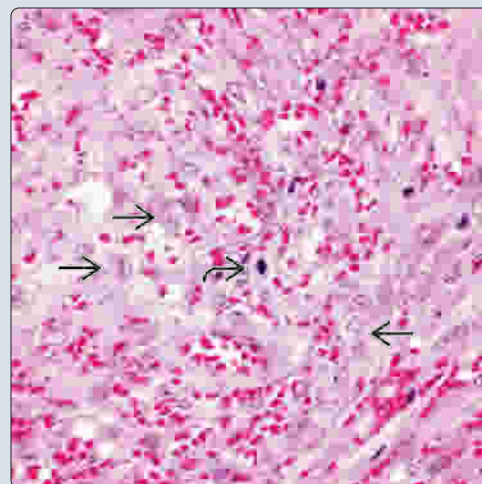
- Warthin-Starry staining shows granular material to contain bacilli which appear slender, located interstitially

Cervical Neck Lymph Node Involvement

(Left) A lymph node shows partial replacement by a well-circumscribed, solid to lobular proliferation. A portion of the lymph node parenchyma is present. (Right) At higher magnification, the node is replaced by a vascular proliferation comprised of variably sized blood vessels lined by prominent plump-appearing endothelial cells; mitotic figures can be identified. These findings may suggest a diagnosis of Kaposi sarcoma or an angiosarcoma.

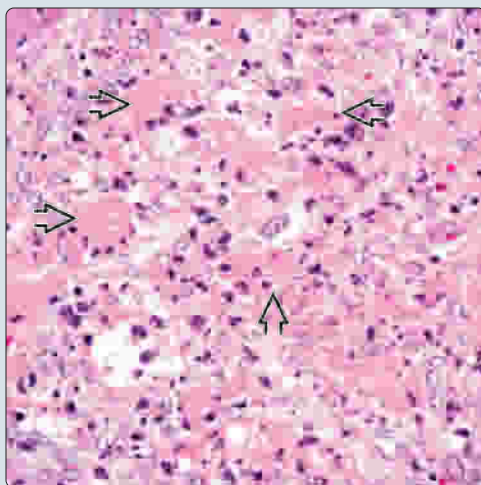


Intranodal Vascular Proliferation

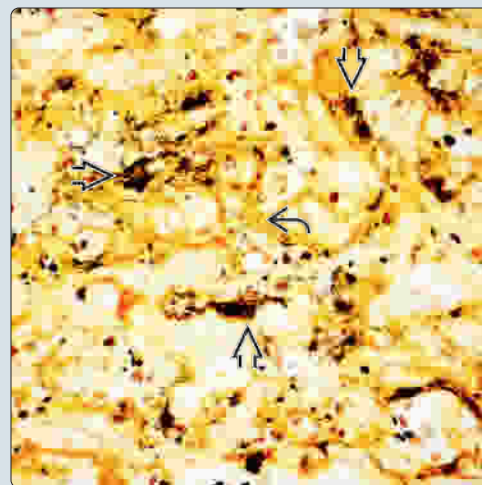


Granular Eosinophilic Clumps

(Left) The presence of neutrophils and neutrophilic debris seen adjacent to the capillary proliferation, as well as the presence of granular eosinophilic appearing clumps associated with neutrophils corresponding to masses of bacilli, is a key histologic clue to the diagnosis of bacillary angiomatosis (BA). (Right) Warthin-Starry staining shows the presence of slender-appearing bacilli representing the *Rochalimaea* species (*Rochalimaea henselae*). Bacilli also form the darker staining clumps.



Warthin-Starry Positive Organisms



TERMINOLOGY

Abbreviations

- Bacillary angiomatosis (BA)

Definitions

- Pseudoneoplastic capillary proliferative lesion that occurs as complication of HIV infection and usually presents as cutaneous vascular lesion

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Caused by *Rochalimaea* species (*Rochalimaea henselae*) as well as by *Bartonella quintana*
- Occurs most often in immunocompromised patients but may occur in patients with intact immune system
 - May occur in association with Kaposi sarcoma and in solid organ transplant recipients (adults and pediatric patients)

CLINICAL ISSUES

Epidemiology

- Age
 - Occurs over wide age range (from young to old)
- Sex
 - Equal gender distribution

Site

- Most commonly presents as cutaneous or mucocutaneous lesion
- May involve other organs sites, including lymph nodes, spleen, liver as well as mucosal sites of upper respiratory tract and conjunctiva

Presentation

- Commonly associated with systemic symptoms, including fever, chills, weight loss, and night sweats
- Multiple erythematous papules ± crusting

Laboratory Tests

- Serologic demonstration of antibodies by direct immunofluorescence and enzyme immunoassay
- Proteomic analysis with identification of immunoreactive antigens found to be useful for improved *Bartonella*-specific serodiagnosis

Treatment

- Options, risks, complications
 - Full dose erythromycin

Prognosis

- Antibiotic therapy is effective, often resulting in resolution of lesions
- If left untreated, may be progressive and potentially life threatening

MICROSCOPIC

Histologic Features

- Well-circumscribed lobular capillary proliferation
- Small capillaries arranged around ectatic vessels lined by prominent endothelial cells

- Endothelial cells appear hyperchromatic and pleomorphic
- Solid areas may be present and may obscure vascular proliferation
- Mitotic figures, including atypical forms and necrosis, may be present
- Presence of neutrophils and neutrophilic debris adjacent to capillary proliferation
 - Granular clumps associated with neutrophils correspond to masses of bacilli
- Overlying epithelium may be ulcerated or thinned or show pseudoepitheliomatous hyperplasia

ANCILLARY TESTS

Histochemistry

- Warthin-Starry staining shows granular material to contain bacilli, which appear slender, located interstitially

DIFFERENTIAL DIAGNOSIS

Hemangioma (Lobular Capillary, Epithelioid)

- Lacks clusters of bacilli

Angiosarcoma

- Interconnecting, ramifying vascular channels with vascular tufting, atypical endothelial cells, increased mitoses

Kaposi Sarcoma

- Spindled cells, interconnecting vascular channels, extravasated red cells, hyaline globules; HHV8(+)

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KEY FACTS

TERMINOLOGY

- Pseudoneoplastic spindle cell proliferation caused by *Mycobacterium avium-intracellulare* and almost exclusively occurring in HIV(+) patients
- Synonyms include: Mycobacterial pseudotumor; *M. avium-intracellulare* pseudotumor; spindled nontuberculous mycobacteriosis; histoid mycobacteriosis

ETIOLOGY/PATHOGENESIS

- Causative microorganism is *M. avium-intracellulare*
- Almost always found in immune-compromised individuals
 - AIDS/HIV(+) patients; patients receiving immunosuppressive therapy

CLINICAL ISSUES

- Common site of occurrence include lymph nodes
 - Extranodal sites may include skin, spleen, brain, bone marrow

- Rarely occur in mucosal sites of upper aerodigestive tract (nasal septum)
- Treatment guidelines are based on species of mycobacteria and susceptibility testing of isolate

MICROSCOPIC

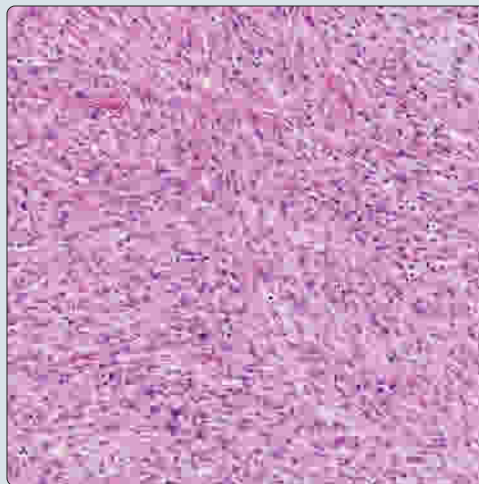
- Cellular proliferation of bland spindle-shaped cells in storiform pattern
 - Spindle cells represent histiocytes
- Absence of granuloma formation
 - Multinucleated giant cells and foamy histiocytes are not present
- Partial or complete effacement of nodal or mucosal architecture

ANCILLARY TESTS

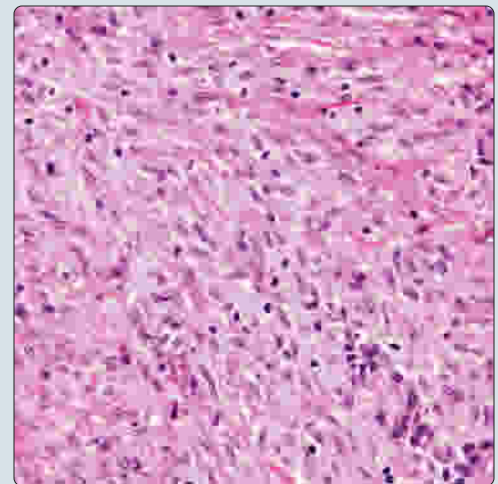
- Presence of numerous acid-fast bacilli (+) organisms within cytoplasm of spindle cells
- Spindle cells are positive for CD68, lysozyme, α -1-antichymotrypsin, and vimentin

(Left) At low magnification, the presence of fascicular to storiform growth comprised of spindle-shaped cells suggests a possible diagnosis of a mesenchymal tumor and may not lead to the consideration of a mycobacterial spindle cell pseudotumor. (Right) This immunocompromised patient presented with lymphadenopathy. Histologically, the lymph node is replaced by a bland spindle cell proliferation without features of classic mycobacterial infection (e.g., well-formed caseating granulomatous inflammation).

Cervical Neck Spindle Cell Proliferation

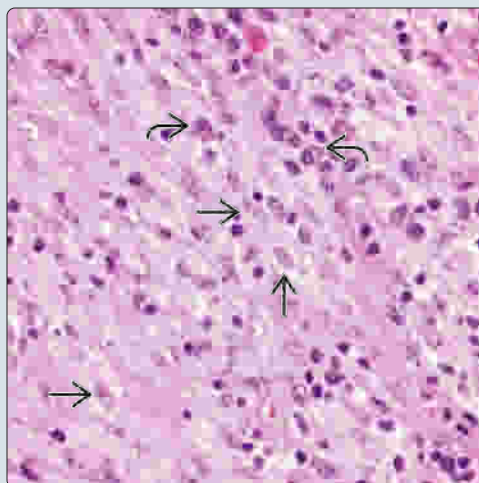


Spindle Cell Proliferation

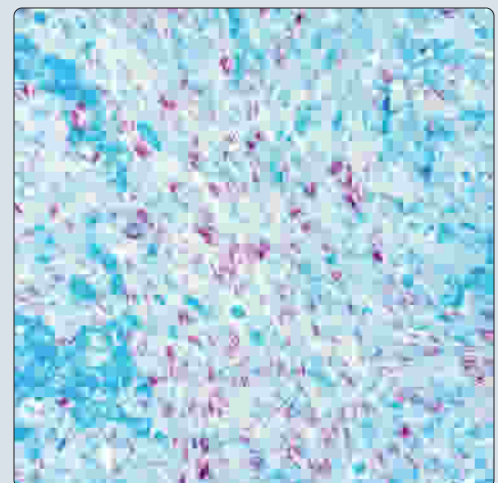


(Left) An admixed inflammatory cell infiltrate including lymphocytes and plasma cells may be present and can obscure the bland spindle-shaped lesional cells. There is an absence of granuloma formation &/or multinucleated giant cells. (Right) Ziehl-Neelsen stain shows the presence of numerous positive (red) mycobacteria in the cytoplasm of the spindled cells. The main diagnostic clue is the history of immunosuppression.

Admixed Inflammatory Cells



Mycobacterial Organisms



TERMINOLOGY

Synonyms

- Mycobacterial pseudotumor; *Mycobacterium avium-intracellulare* pseudotumor; spindled nontuberculous mycobacteriosis; histoid mycobacteriosis

Definitions

- Pseudoneoplastic spindle cell proliferation caused by *M. avium-intracellulare* and almost exclusively occurring in HIV(+) patients

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Causative microorganism is *M. avium-intracellulare*
 - Almost always found in immune-compromised individuals
 - AIDS/HIV(+) patients; patients receiving immunosuppressive therapy

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon
- Age
 - Occurs over wide age range
- Sex
 - Equal gender distribution

Site

- Lymph nodes
- Extranodal sites
 - Skin, spleen, brain, bone marrow
 - Rarely occur in mucosal sites of upper aerodigestive tract (nasal septum)

Presentation

- Subcutaneous or submucosal firm nodule; lymphadenopathy

Treatment

- Options, risks, complications
 - Treatment guidelines are based on species of mycobacteria and susceptibility testing of isolate
 - In some cases would be modified because of immune status of patient or other concurrent therapy
 - If no isolate is obtained, recommendation would be to treat for tuberculosis

MICROSCOPIC

Histologic Features

- Cellular proliferation composed of bland-appearing spindle-shaped cells in storiform pattern
 - Spindle cells represent histiocytes
- Absence of granuloma formation
 - Multinucleated giant cells and foamy histiocytes typically not present
 - Necrotic foci may be present
- Associated lymphocytes and plasma cells present

- Partial or complete effacement of nodal or mucosal architecture

ANCILLARY TESTS

Histochemistry

- Acid-fast bacilli (AFB) or Ziehl-Neelsen stain
 - Presence of numerous AFB(+) organisms within cytoplasm of spindle cells

Immunohistochemistry

- Spindle cells **positive**: CD68, lysozyme, α-1-antichymotrypsin, and vimentin
- Possibly **positive**: S100 protein, desmin, and muscle-specific actin
- **Negative**: CD31, CD34, and HHV-8

Genetic Testing

- PCR used in identification of mycobacteria

DIFFERENTIAL DIAGNOSIS

Kaposi Sarcoma

- May occur concomitantly (in same lymph node) as mycobacterial spindle cell tumor
- Morphologic features include
 - Prominent fascicular arrangement of spindle cells with slit-like spaces
 - Extravasated red cells, hyaline globules, increased mitoses
 - **Positive**: CD34, podoplanin, HHV-8; **negative**: CD68

Fibrohistiocytic Neoplasm

- Typically includes multinucleated cells
- Absence of mycobacteria

Hodgkin Lymphoma, Nodular Sclerosing

- CD30, CD15 immunoreactivity; EBV(+) (10-40%)
- Absence of mycobacteria

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KEY FACTS

TERMINOLOGY

- Multisystem chronic granulomatous disease of unknown etiology; diagnosis based on excluding infectious disease

ETIOLOGY/PATHOGENESIS

- Remains unknown but there is increasing evidence of finding mycobacterial DNA by polymerase chain reaction in sarcoid granulomas

CLINICAL ISSUES

- Occurs in all age groups but most commonly seen in young adults; peak incidence: 2nd-4th decades
- Blacks > > whites (12:1)
- Any organ may be affected but most commonly lung, lymph nodes, skin
- Isolated extranodal head and neck involvement only occurs in small percentage of cases
- Most common clinical presentation includes fever, weight loss, and hilar adenopathy

- Elevated angiotensin-converting enzyme levels
- Treatment for symptomatic patients is with corticosteroid therapy
- ~ 70% improve or remain stable following therapy; ~ 10-20% do not respond to therapy

MICROSCOPIC

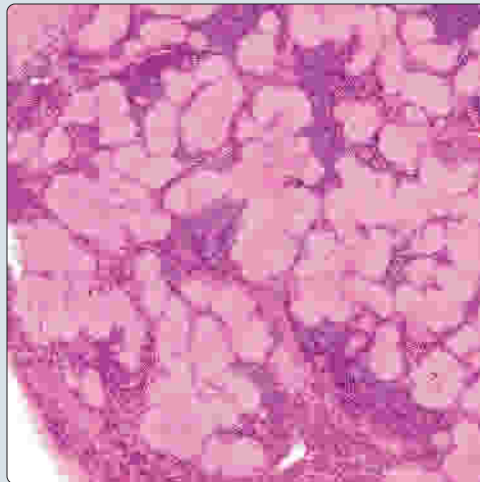
- Multiple well-formed, noncaseating granulomas consisting of nodules of epithelioid histiocytes surrounded by mixed inflammatory infiltrate
- Langerhans-type giant cells may be present
- Necrosis absent but some examples, especially extranodal, may have small central foci of necrosis
- Intracytoplasmic, star-shaped inclusions (asteroid bodies) &/or calcific laminated bodies (Schaumann bodies) may be seen

ANCILLARY TESTS

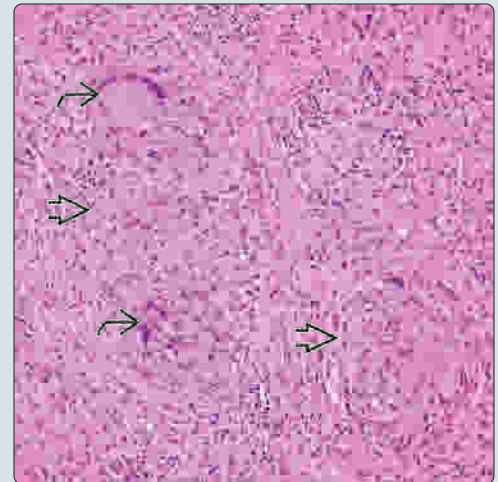
- Special stains for microorganisms are negative

Cervical Node Granulomatous Inflammation

(Left) At low magnification, the lymph node architecture is mostly effaced/replaced by multiple well-formed, confluent-appearing granulomas. Residual lymph node parenchyma is seen in and around the granulomatous inflammatory process. **(Right)** Multiple well-formed, noncaseating granulomas composed of nodules of epithelioid histiocytes are present surrounded by a mixed inflammatory infiltrate; Langerhans-type giant cells are seen.



Noncaseating Granulomatous Inflammation

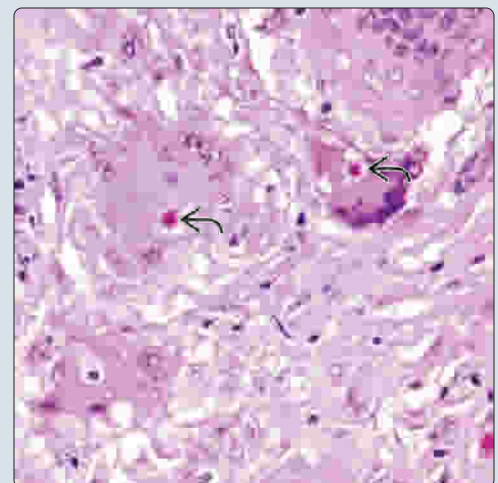


Noncaseating Granulomatous Inflammation

(Left) At higher magnification, this well-formed, noncaseating granuloma consists of epithelioid histiocytes, including Langerhans-type giant cells. Histochemical stains evaluating for the presence of microorganisms were negative (not shown). **(Right)** Intracytoplasmic, star-shaped asteroid bodies are seen in Langerhans-type giant cells, supporting a diagnosis of sarcoidosis. Additional findings may include intracytoplasmic calcific laminated bodies, referred to as Schaumann bodies (not shown).



Asteroid Bodies



TERMINOLOGY

Definitions

- Multisystem chronic granulomatous disease of unknown etiology

ETIOLOGY/PATHOGENESIS

Etiology

- Remains unknown but increasing evidence of finding mycobacterial DNA by polymerase chain reaction in sarcoid granulomas
- Sarcoidosis and sarcoid-like reactions may occur in association with head and neck cancer (synchronously or metachronously) and may also occur after chemotherapy

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon
- Age
 - Occurs in all age groups but most commonly seen in young adults; peak incidence: 2nd-4th decades
- Sex
 - Female predominance (slight)
- Ethnicity
 - Blacks > > whites (12:1)

Site

- Any organ may be affected but most commonly lung, lymph nodes, skin
- Isolated extranodal head and neck involvement only occurs in small percentage of cases and includes
 - Pharynx, tonsils, sinonasal tract, larynx, salivary glands, ear/temporal bones, thyroid gland, parathyroid glands
 - Salivary gland involvement referred to as Heerfordt syndrome or uveoparotid fever

Presentation

- Most common clinical presentation includes fever, weight loss, and hilar adenopathy
- Otolaryngic symptoms vary according to site and include
 - Cervical adenopathy, pharyngotonsillitis with tonsillar enlargement, nasal obstruction, nasal discharge, epistaxis, septal perforation
 - Salivary gland involvement may
 - Clinically simulate Sjögren syndrome with enlargement, xerostomia, and xerophthalmia
 - Present with facial nerve paralysis

Laboratory Tests

- Elevated angiotensin-converting enzyme levels
- Cutaneous anergy to skin test antigens (Kveim test) positive in 60-85% of patients

Treatment

- Options, risks, complications
 - Treatment for symptomatic patients is with corticosteroid therapy
- Surgical approaches
 - May be necessary in presence of severe airway obstruction

Prognosis

- Prognosis generally good
 - ~ 70% improve or remain stable following therapy; ~ 10-20% do not respond to therapy

MICROSCOPIC

Histologic Features

- Multiple well-formed, noncaseating granulomas consisting of nodules of epithelioid histiocytes surrounded by mixed inflammatory infiltrate
 - Langhans-type giant cells may be present
 - Necrosis absent but some examples, especially extranodal, may have small central foci of necrosis
 - Intracytoplasmic, star-shaped inclusions (asteroid bodies) &/or calcific laminated bodies (Schaumann bodies) may be seen

ANCILLARY TESTS

Histochemistry

- Special stains for microorganisms are negative

Genetic Testing

- Major histocompatibility complex (MHC) genes and non-MHC genes located on short arm of chromosome 6 implicated as genetic risk factors

DIFFERENTIAL DIAGNOSIS

Infectious Diseases

- Noncaseating granulomatous inflammation can be seen in tuberculosis (typical and atypical), fungal diseases, leprosy, cat scratch disease, other infectious diseases

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KEY FACTS

TERMINOLOGY

- Mass-forming myofibroblastic proliferation displaying tissue culture-like growth pattern

ETIOLOGY/PATHOGENESIS

- Trauma may be slight and limited, overlooked by patient
- Inducible and reversible recurrent somatic gene fusion: *MYH9-USP6*

CLINICAL ISSUES

- Uncommon, with 30% of cases in head and neck
- Children and young adults (≤ 35 years)
- Rapidly growing mass of short duration (< 3 weeks)

MACROSCOPIC

- Unencapsulated, round to oval, nodular mass, frequently attached to fascia
- Cut surfaces range from firm to soft and gelatinous, depending on duration

MICROSCOPIC

- Poorly circumscribed with irregular stellate appearance
- Plump myofibroblasts in tissue culture-like appearance
- Arranged in storiform, short, irregular interlacing fascicles and bundles
- Easily identified mitotic figures, but never atypical
- Background of extravasated erythrocytes, inflammatory cells, and giant cells
- Keloid-like collagen deposition

ANCILLARY TESTS

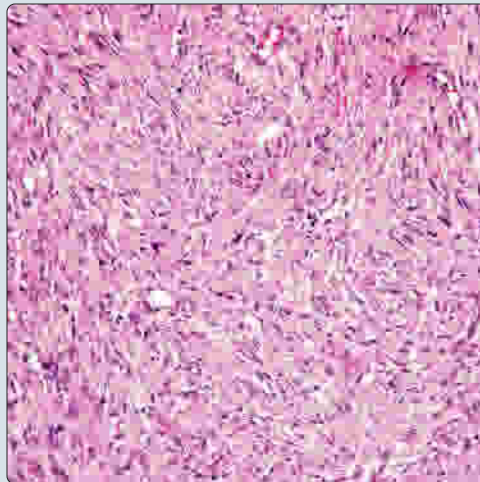
- **Positive:** Actins, vimentin; CD68 (histiocytes)
- Cytology: Cellular smears with interlaced short, plump spindled fibroblasts in slightly myxoid background, with mitoses

TOP DIFFERENTIAL DIAGNOSES

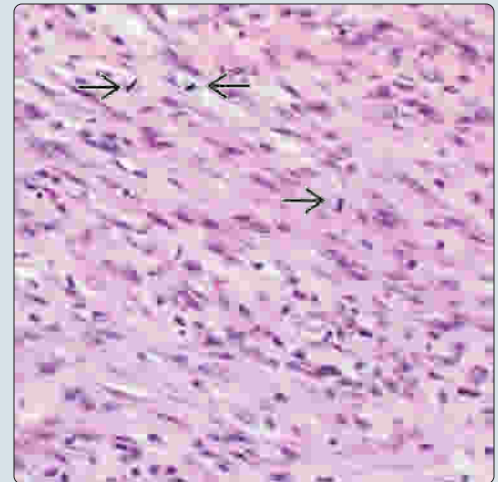
- Fibrosarcoma, rhabdomyosarcoma, fibromatosis, fetal rhabdomyoma, pleomorphic adenoma, myoepithelioma

Storiform Growth With Collagen Deposition

(Left) Hematoxylin & eosin shows keloid-like collagen deposition within a proliferation of spindled fibroblasts. The cells are arranged in short, interlacing fascicles. Extravasated erythrocytes are noted. (Right) There are remarkably increased numbers of mitoses in nodular fasciitis, but they are not atypical. The spindled cells do not show any pleomorphism.

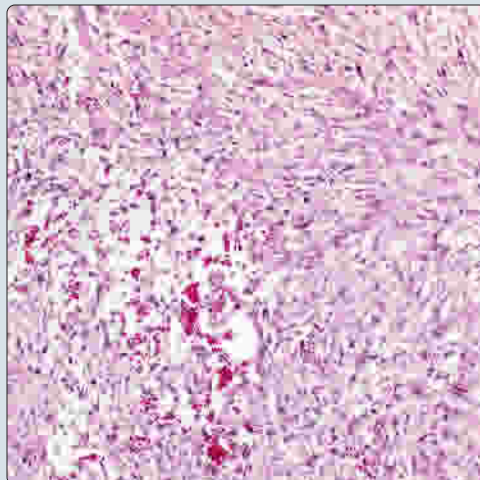


Increased Mitoses in Nodular Fasciitis

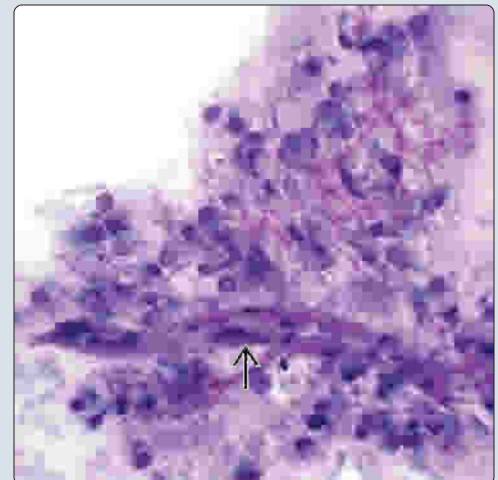


Tissue Culture-Like Growth With Blood

(Left) The cells are arranged in a tissue culture-like appearance with myxoid change, extravasated erythrocytes, and keloid-like collagen deposition. (Right) The bipolar fibroblasts show abundant cytoplasm eccentrically pulled off to one side of the cells. Note the capillaries that are part of the smear in this example of nodular fasciitis.



Bipolar Cells Associated With Vessels



TERMINOLOGY

Synonyms

- Cranial fasciitis; intravascular fasciitis

Definitions

- Mass-forming myofibroblastic proliferation displaying tissue culture-like growth pattern

ETIOLOGY/PATHOGENESIS

Trauma

- May be slight and limited, overlooked by patient

Neoplasm

- Inducible and reversible recurrent somatic gene fusion: *MYH9-USP6*

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon, with 30% of cases in head and neck
- Age
 - Children and young adults (≤ 35 years)
 - Rare in elderly (> 60 years)
- Sex
 - Equal gender distribution

Site

- Upper extremities and neck
- Uncommon: Face, orbit, oral cavity, salivary glands

Presentation

- Rapidly growing mass
- Short duration (< 3 weeks)

Natural History

- Spontaneous involution with time

Treatment

- Simple excision

Prognosis

- Recurs in 2%, although potentially persistent

MACROSCOPIC

General Features

- Unencapsulated, round to oval, nodular mass, frequently attached to fascia
- Cut surfaces range from firm to soft and gelatinous, depending on duration
- Cystic areas common

Size

- Mean: < 3 cm, although up to 5 cm

MICROSCOPIC

Histologic Features

- Poorly circumscribed with irregular stellate appearance
- Plump myofibroblasts in tissue culture-like appearance
- Arranged in storiform, short, irregular interlacing fascicles and bundles

- Benign myofibroblasts with oval nuclei, pale chromatin, and prominent nucleoli
- Easily identified mitotic figures, but never atypical
- Background of extravasated erythrocytes, inflammatory cells, and giant cells
- Keloid-like collagen deposition
 - More collagen with lesions of longer duration

ANCILLARY TESTS

Cytology

- Cellular smears with interlaced short, plump spindled fibroblasts in slightly myxoid background
- Fibroblasts with eccentric nuclear placement, occasionally binucleated
- Mitotic figures may be seen
- Clumps of collagen in background

Immunohistochemistry

- **Positive:** Actins, vimentin; CD68 (histiocytes)

Genetic Testing

- *MYH9-USP6* gene fusion
 - Transient neoplasia caused by recurrent somatic gene fusion of *MYH9* (chromosome 22q12.3-q13) and *USP6* (chromosome 17p13)

DIFFERENTIAL DIAGNOSIS

Fibrosarcoma

- More dense cellularity, herringbone configuration, with atypical mitotic figures

Rhabdomyosarcoma

- Pleomorphic cells, increased mitotic figures, with unique immunohistochemical and molecular profile

Fibromatosis

- Ill-defined, but slender, elongated fibroblasts arranged parallel to vessels and collagen; nuclear β -catenin (+)

Fetal Rhabdomyoma

- Cellular tumor with gradient of cells showing striations

Pleomorphic Adenoma/Myoepithelioma

- Salivary gland: Spindled-epithelioid cells may mimic NF
- **Positive:** Keratin, S100 protein, GFAP, p63

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KEY FACTS

TERMINOLOGY

- Neuroendocrine neoplasm derived from paraganglia composed of chief and sustentacular cells arranged in zellballen pattern

CLINICAL ISSUES

- ~ 30% of all paragangliomas develop in head and neck
 - Carotid body > jugular, tympanic > vagal > larynx
- Female >> male (4-8:1)
- Crotch of common carotid artery bifurcation
- Painless, slowly enlarging neck mass
- Presurgical embolization for reduced bleeding
- Surgery &/or radiation therapy achieves similar outcomes

IMAGING

- Studies show exact location and tumor extent, guide surgical approach, provide therapeutic alternatives

MICROSCOPIC

- Clustered, zellballen, alveolar, or whorled architecture
 - Chief cells: Small to intermediate, epithelioid cells with ample granular, basophilic cytoplasm
 - Nuclei are round to focally irregular and enlarged
 - Sustentacular supporting cells
- Highly vascularized stroma, sometimes with fibrosis
- Malignant tumors are uncommon (document metastases)

ANCILLARY TESTS

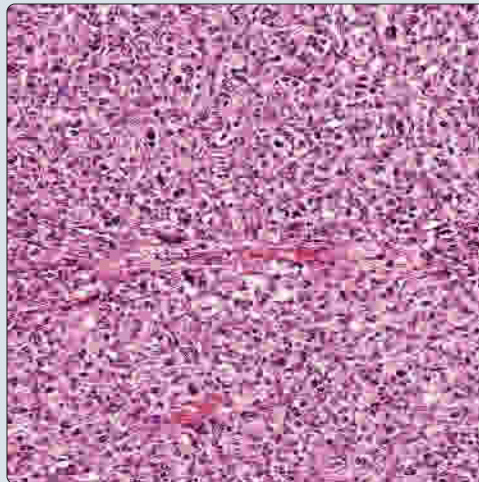
- Chief cells **positive**: Neuroendocrine markers
- Sustentacular cells **positive**: S100 protein, GFAP

TOP DIFFERENTIAL DIAGNOSES

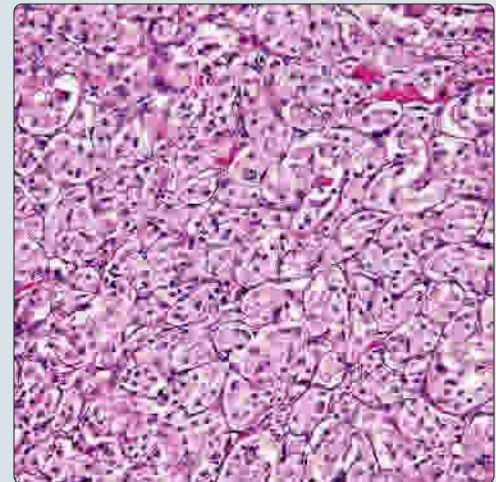
- Medullary thyroid carcinoma
- Schwannoma
- Undifferentiated carcinoma
- Metastatic melanoma

Zellballen Architecture in Paraganglioma

(Left) Clusters and small ball-like (zellballen) configurations are well represented in this paraganglioma. There is a well-developed fibrovascular stroma separating the tumor nests. (Right) The most characteristic pattern of a paraganglioma is the presence of zellballen. Small, well-formed balls of neoplastic cells are separated by a very delicate fibrovascular plexus.

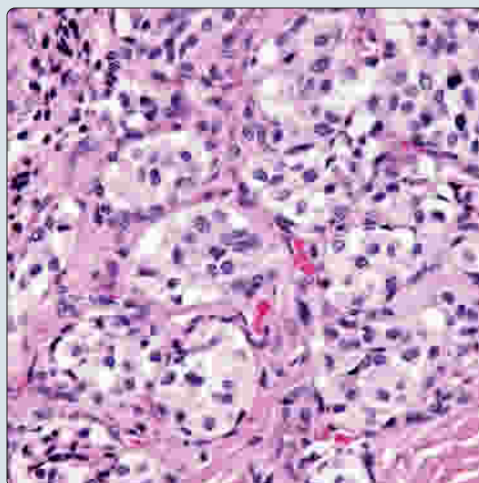


Nested Appearance

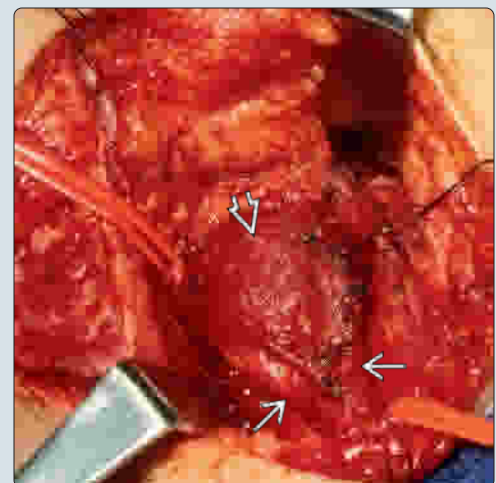


Packeted Cells With No Atypia

(Left) The small- to medium-sized cells have slightly basophilic, delicately granular cytoplasm surrounding round to oval nuclei. The packeted arrangement with surrounding fibrosis is common. (Right) Intraoperative photograph shows splaying of the internal and external carotid arteries [X], as well as a large, richly vascularized tumor [X] set in the crotch of the carotid artery bifurcation.



Intraoperative Tumor at Carotid Bifurcation



TERMINOLOGY

Synonyms

- Chemodectoma, glomus tumor, nonchromaffin paraganglioma, neuroendocrine (NE) tumor

Definitions

- NE neoplasm derived from **carotid body** paraganglia composed of chief and sustentacular cells arranged in characteristic (zellballen) pattern

ETIOLOGY/PATHOGENESIS

Etiology

- Familial inheritance
 - Hereditary paraganglioma: Autosomal dominant with inactivating germline mutations in succinate dehydrogenase (SDH) complex (*SDHD*, *SDHC*, *SDHB* genes): Seen in ~ 30% of patients
 - SDH* genes encode subunits of SDH complex, part of mitochondrial respiratory chain (complex II) of Krebs cycle
 - Type 1: *SDHD* (most common in head and neck)
 - Type 3: *SDHC*
 - Type 4: *SDHB* gene mutations (malignant cases)
 - Rarely, von Hippel-Lindau syndrome, neurofibromatosis type 1 (*NF1*), *RET* (multiple endocrine neoplasia type 2A and 2B), *TMEM127*, *SDHAF2*
- Chronic hypoxia is known risk factor
 - Tumors are increased in frequency in patients living at high altitudes
 - Women (presumably due to menstruation) show greater hypoxia at high altitudes
 - Athletic patients and patients with large lung capacity may overcome hypoxia

Pathogenesis

- Paraganglia are aggregates of specialized NE tissue (glomus cells)
 - Arise from embryonic neural crest (part of sympathetic nervous system)
 - Found at bifurcation of common carotid artery
- Function as chemoreceptors
 - Respond to acute changes in oxygen tension, carbon dioxide levels, and hydrogen ion concentration

CLINICAL ISSUES

Epidemiology

- Incidence
 - Incidence of ~ 1:300,000
 - ~ 30% of all paragangliomas develop in head and neck
 - Carotid body > jugular, tympanic > vagal > larynx
 - Rule of 10s: 10% multicentric, bilateral, pediatric, &/or malignant; ~ 30% familial
- Age
 - Mean: 40-50 years
 - Rare in children, except if familial
 - Malignant cases tend to be younger
- Sex
 - Female > male (4-8:1)
 - Male > female for inherited/familial tumors

Site

- Crotch of common carotid artery bifurcation
 - Between external carotid artery (ECA) and internal carotid artery (ICA)

Presentation

- Painless (asymptomatic), slowly enlarging neck mass
 - Shows easy side-to-side movement (Fontaine sign) but no vertical movement
 - Pain and rapidly enlarging mass are more frequently seen in malignant cases
- Cranial nerve (CN) paresis or paralysis with larger tumors
- Infrequently associated with dysphagia, hoarseness, headache, Horner syndrome, syncope
- Bruit or thrill may be present
- Catecholamine function is very rare
- If familial or syndromic cases
 - Autosomal dominant trait with genomic imprinting
 - More commonly bilateral (30%) &/or multifocal
 - Rare association with clotting factor VII and X deficiencies

Laboratory Tests

- < 3% of tumors secrete catecholamines that result in clinical symptoms

Treatment

- Options, risks, complications
 - Do not biopsy:** Very vascularized with heavy bleeding
 - Presurgical embolization reduces bleeding, which is otherwise common complication
 - Complications include: First bite syndrome, CN deficits (22%), artery resection, Horner syndrome, ipsilateral vagal nerve loss, stroke; rarely death
- Surgical approaches
 - Surgery, including 1 or more branches of carotid artery system, is treatment of choice
- Radiation
 - Radiotherapy can be used for localized tumors
 - Same control as surgery with fewer deficits
- Molecular-targeted therapies
 - New molecular-based therapies show promise
- Observation only
 - ~ 40% of tumors remain stable, and up to 20% regress (during 5-year follow-up)
 - Tumors grow ~ 0.2 cm per year

Prognosis

- Excellent overall outcome because tumors are slow growing
- Up to 10% will recur (inadequate excision and regrowth); more common with *SDHB*-mutated tumors
- Mortality due to proximity with vital anatomic structures
- Malignant tumors are uncommon (~ 10%)
 - Cervical lymph nodes (90% of time), lung and bone (10%) metastases
 - 5-year survival rates: ~ 88% for malignant tumors (surgery alone); ~ 95% if regional disease only (surgery alone)
 - Favorable** factors: Regional **instead** of distant metastasis; surgery alone; carotid body site; **unfavorable** factors: Age > 50 years

Shamblin Classification of Carotid Body Tumors

Shamblin Class I	Shamblin Class II	Shamblin Class III
Carotid body tumor with splaying of carotid bifurcation, but little attachment to vessels	Carotid body tumor partially surrounding internal and external carotid artery	Carotid body tumors intimately surround carotid arteries
Complete resection with very little morbidity	Complete resection more challenging	Resection may require major vessel reconstruction

Shamblin WR et al: Carotid body tumor (chemodectoma). Clinicopathologic analysis of ninety cases. Am J Surg. 122(6):732-9, 1971.

IMAGING

Radiographic Findings

- Imaging studies show exact location and tumor extent, guide surgical approach, and provide therapeutic alternatives
- Avidly enhancing vascular mass splaying ECA and ICA, displacing ICA posterolaterally
- **Angiography:** Hypervascular mass at carotid artery bifurcation
 - Allows for presurgical embolization
- Octreotide or MIBG scintigraphy for occult or familial tumors
- PET with F18-FDG: Avid uptake by tumor cells

Ultrasonographic Findings

- Solid mass; color Doppler flow shows extensive vascularity

MR Findings

- T1WI: "Salt and pepper" appearance when > 1.5 cm, hypointense punctate flow channels due to tumor vascularity
- T2WI with contrast: Intense enhancement, larger high-velocity flow voids

MACROSCOPIC

General Features

- Firm, rubbery, well-circumscribed, polypoid mass
- Variegated cut surface, red, yellow, tan, pink, or brown
- May be large and widely invasive

Size

- Range: 1-6 cm (mean: 4 cm)

MICROSCOPIC

Histologic Features

- Clustered, zellballen, alveolar, or whorled architecture
- Highly vascularized stroma, sometimes with fibrosis
- Poorly encapsulated or circumscribed, often infiltrative
 - Vascular and perineural invasion uncommon but not prognostically significant
- Moderately cellular, biphasic tumor
- Cyst formation, hemorrhage, and hemosiderin-laden macrophages common
- Paraganglia (chief) cells (type I)
 - Small to intermediate, epithelioid cells with ample granular, basophilic cytoplasm
 - Nuclei are round to focally irregular and enlarged
 - Delicate to coarse nuclear chromatin
 - Rarely, multinucleated giant cells and spindled cells

- Sustentacular supporting cells (type II)
 - Create net or supporting framework surrounding nests
 - Cannot be detected without stains (S100 protein, GFAP)
- Mitotic figures are very rare
- Malignant tumors are uncommon (up to 10%)
 - Malignant if documented metastases
 - Histology does not predict clinical behavior

ANCILLARY TESTS

Cytology

- Fine-needle aspiration usually contraindicated, as it may provoke hypertensive crisis or significant bleeding

Immunohistochemistry

- Chief cells **positive:** Synaptophysin, chromogranin-A, CD56, NSE
- Sustentacular cells **positive:** S100 protein, GFAP
- **Negative:** Pan-cytokeratin, carcinoembryonic antigen

Genetic Testing

- Genetic counseling and testing for *SDHX*, *VHL*, *NF1*, and *RET* genes should be offered to all patients with paraganglioma

DIFFERENTIAL DIAGNOSIS

Medullary Thyroid Carcinoma

- Thyroid mass, frequently with neck metastases
- Spindled epithelioid cells with round to irregular nuclei and "salt and pepper" nuclear chromatin distribution
- **Positive:** Calcitonin, pan-cytokeratin, TTF-1, CEA-M

Schwannoma

- Spindle cells, cellular and hypocellular areas
- **Positive:** S100 protein, SOX10

Undifferentiated Carcinoma

- Specifically metastatic tumor to neck
- **Positive:** Strong keratin; **negative:** S100 protein, NE markers

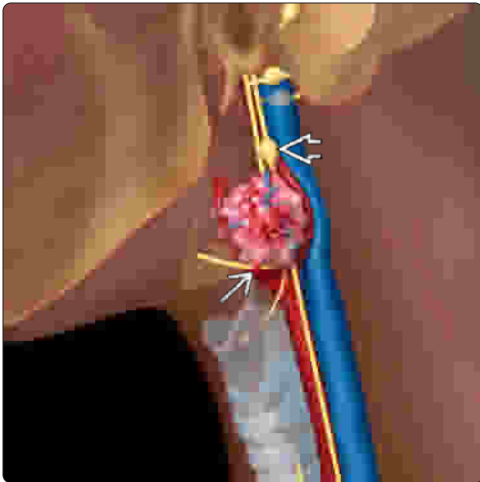
Metastatic Melanoma

- Histologic mimic; pigmented; intranuclear cytoplasmic inclusions
- **Positive:** S100 protein, SOX10, HMB-45; **negative:** Keratin, NE markers

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Graphic of Nerve and Vessel Relationships



Carotid Artery Angiography



(Left) Graphic shows a carotid body paraganglioma splaying the external and internal carotid arteries. The main arterial feeder is the ascending pharyngeal artery. The glomus bodies are illustrated in the nodose ganglion of CN10. (Right) Lateral common carotid angiogram demonstrates intense carotid body paraganglioma tumor blush between the external and internal carotid arteries. Angiography also allows for presurgical embolization.

CT of Avidly Enhancing Paraganglioma



Malignant Paraganglioma With Lymph Node Metastases

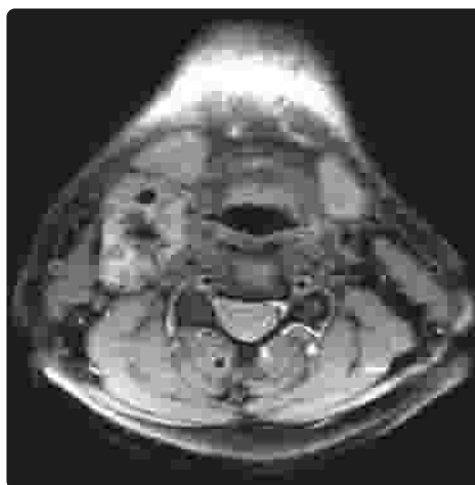


(Left) Axial contrast-enhanced CT shows a classic example of carotid body paraganglioma as an avidly enhancing mass splaying external and internal carotid arteries at the carotid bifurcation. (Right) Sagittal contrast-enhanced CT shows a large carotid body paraganglioma as an avidly enhancing mass extending up to the skull base. Note the enlarged lymph nodes, confirming the presence of a malignant tumor.


Bilateral Carotid Body Tumors



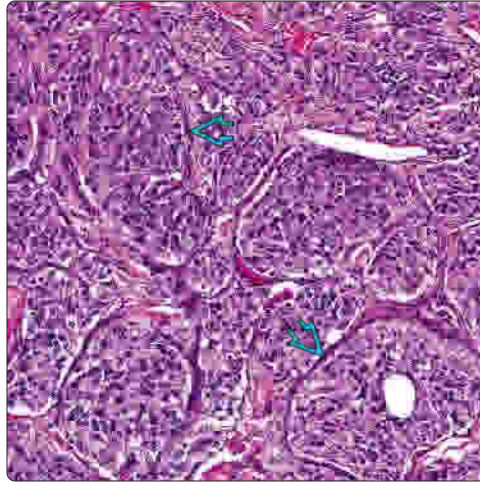
MR of Carotid Body Tumor Encasing the Arteries



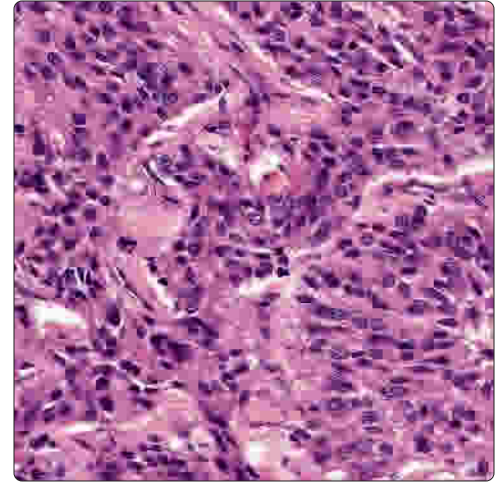
(Left) Bilateral carotid body tumors in this axial contrast-enhanced CT show an avidly enhancing mass at the level of the bifurcation of the carotid arteries on both sides. (Right) Fat-suppressed MR T2WI shows complete encasement of the internal and external carotid arteries by a large hyperintense mass. On removal, this case was a malignant paraganglioma.

(Left) Paraganglioma, especially within the carotid body, can have larger nests of cells , separated by a fibrovascular plexus. Cellular pleomorphism is frequently present within these larger nests. They do not equate to malignancy, however. **(Right)** The nested pattern is composed of cells that have more of a spindled appearance. The cytoplasmic quality is similar, with hyperchromatic nuclear chromatin.

Larger Cell Nests

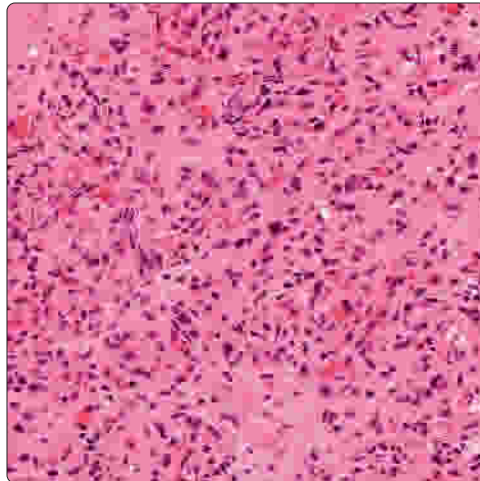


Focal Tumor Cell Spindling

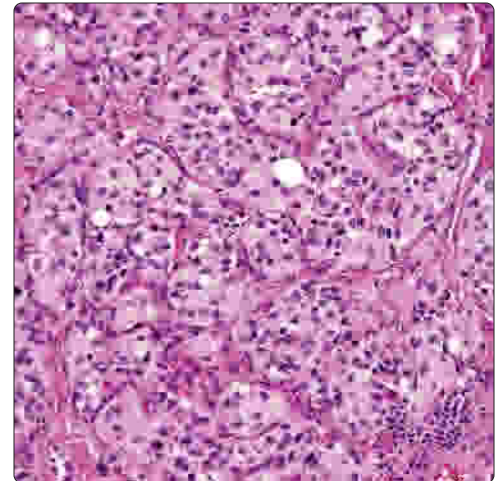



(Left) In many tumors, the zellballen architecture can sometimes be subtle, instead showing a more sheet-like distribution. The nuclei show vague pleomorphism in a few cells. **(Right)** Cell nesting is one of the most characteristic appearances of paraganglioma. The cytoplasm of these tumor cells is abundant, showing a more eosinophilic appearance than usual. There are fibrovascular septa surrounding the paraganglia cells.

Sheet-Like Distribution in Paraganglioma

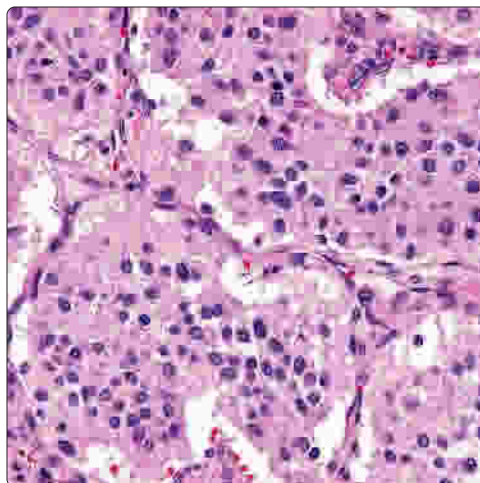


Abundant Eosinophilic-Granular Cytoplasm

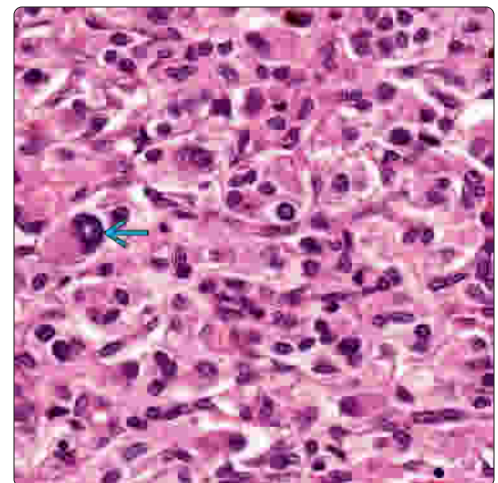


(Left) This high-power image demonstrates a syncytial arrangement of the neoplastic cells. There are delicate fibrovascular septa around the tumor nests. The nuclei show coarse but salt and pepper nuclear chromatin distribution. **(Right)** Most neoplastic cells have a bland appearance, with round to oval hyperchromatic nuclei. However, isolated neoplastic cells will show pleomorphism .

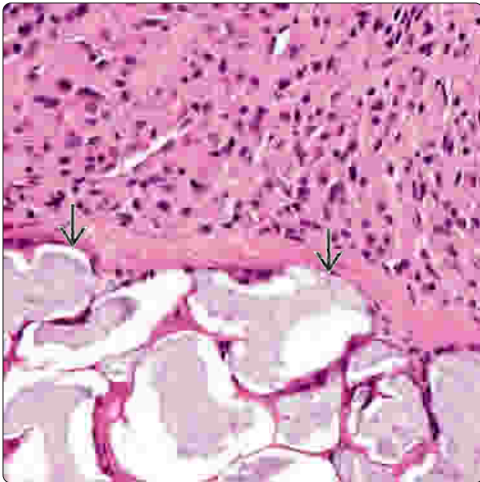
Syncytial Architecture



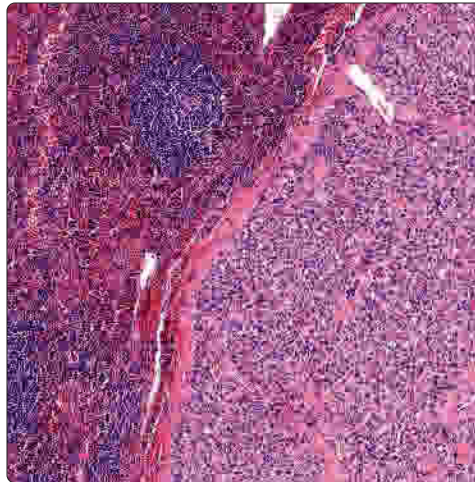
Isolated Nuclear Pleomorphism



Embolic Material Within Paraganglioma

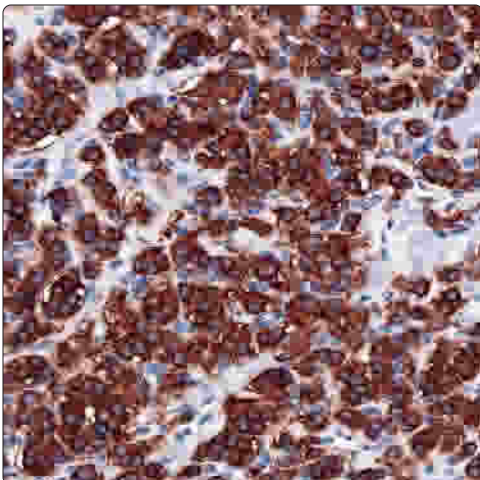


Lymph Node Metastasis

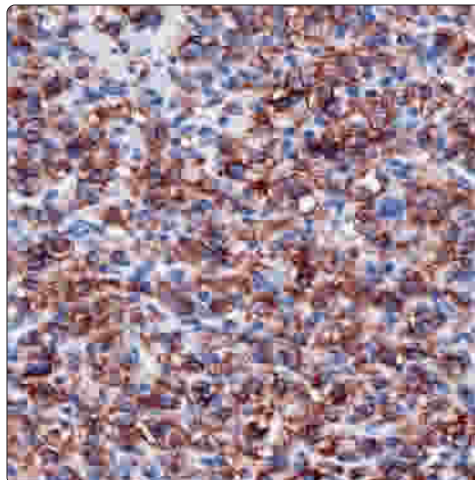


(Left) Tumor architecture is very difficult to determine in this field. There is a foreign body giant cell reaction to the embolic material within this tumor, which was preoperatively embolized to decrease bleeding. (Right) Malignant paraganglioma is usually confirmed by the presence of lymph node metastasis or a tumor in a space where paraganglia are normally not found. Histologic criteria of malignancy (barring metastases) are unreliable, so all paragangliomas are followed long term.

Synaptophysin Reaction

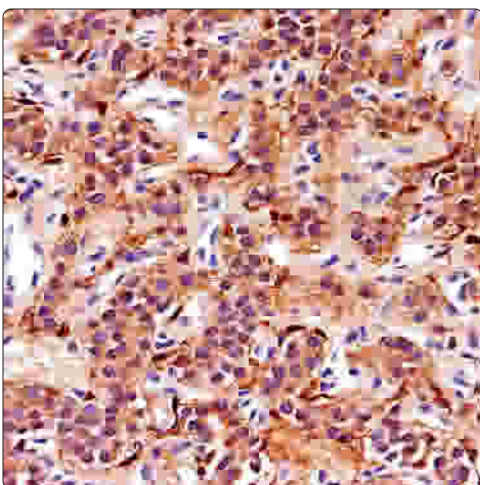


CD56 Membrane-Cytoplasm Reaction

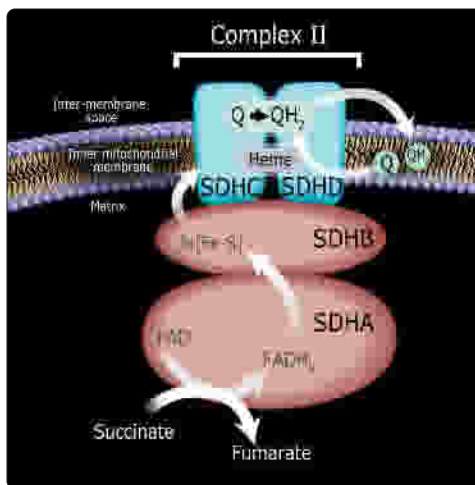


(Left) Synaptophysin is one of the positive neuroendocrine markers in the chief cells (paraganglia cells) of a paraganglioma. Others include chromogranin, CD56, and NSE. (Right) There is a strong and diffuse membrane and partly cytoplasmic reaction with CD56, helping to confirm the neuroendocrine nature of the paraganglia cells.

S100 Protein Sustentacular Reaction



Graphic of the SDH Complex



(Left) S100 protein stains the nucleus and cytoplasm of the peripherally located sustentacular cells. There is often a "blush" or background cytoplasmic reaction that should not be interpreted as positive. (Right) A graphic of part of the mitochondrial respiratory chain complex II shows the relationship between the succinate dehydrogenase ubiquinone oxidoreductase subunits (SDHA → SDHD). Inactivating germline mutations result in hereditary paraganglioma. FAD = flavin adenine dinucleotide.

Elastofibroma

KEY FACTS

TERMINOLOGY

- Ill-defined fibroelastic tumor-like condition comprised of enlarged and irregular elastic fibers

ETIOLOGY/PATHOGENESIS

- Multifocality may suggest systemic enzymatic defect, resulting in abnormal elastogenesis

CLINICAL ISSUES

- Uncommon, reported in < 0.001% of soft tissue tumors
- Elderly patients, nearly exclusively > 50 years old
- Female >> male (5:1)
- Subscapular/infrascapular area, deep to muscle, sometimes attached to periosteum of ribs
- Slow-growing, deep-seated, firm mass, frequently bilateral

MACROSCOPIC

- Ill defined, nonencapsulated, rubbery, and firm

MICROSCOPIC

- Mixture of heavy dense bands of collagenous tissue dissected by fat and abnormal elastic fibers
- Elastic fibers are large (hypertrophic), coarse, thick, and darkly eosinophilic
- Fragmented into linearly arranged globules, simulating beads on string or pipe cleaners
- Degenerated elastic fibers create eosinophilic globules or balls in stroma
- Weigert or von Gieson elastic stains highlight bead-like arrangement

TOP DIFFERENTIAL DIAGNOSES

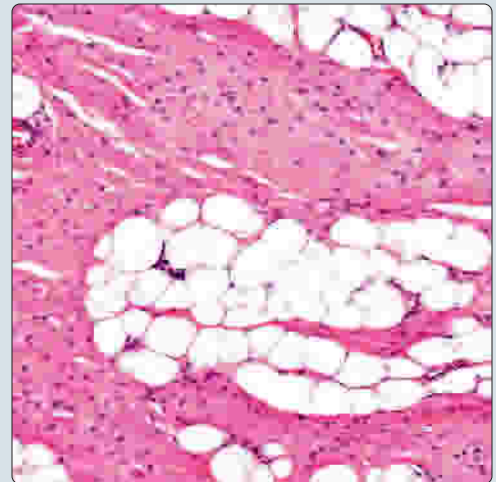
- Spindle cell lipoma
- Nuchal fibroma
- Fibromatosis

Gross Photograph: Elastofibroma

(Left) Gross photograph shows bands of fibrosis dissecting between fat. There is an irregular periphery. These findings are not specific for the tumor. (Right) H&E shows heavy collagen deposition within adipose connective tissue. Degenerated collagen fibers are present, with small balls noted even at this power.

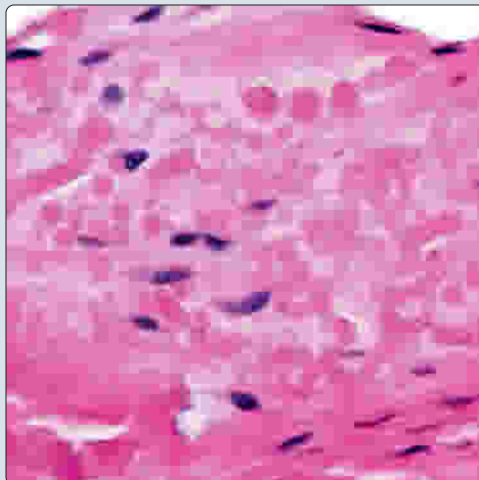


Collagen, Fat, and Elastic Fibers

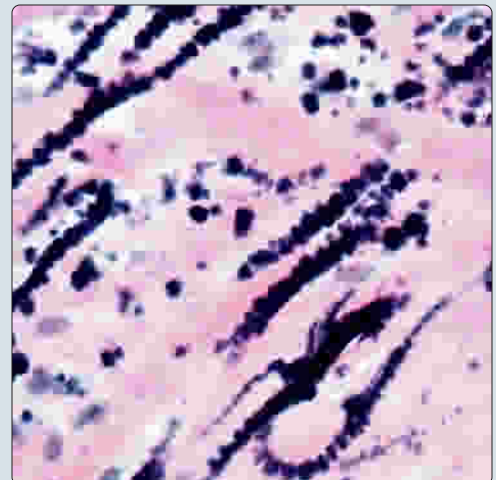


Beads on String Appearance of Collagen

(Left) H&E shows globules of degenerated elastic fibers with collagen. This bead on a string or pipe cleaner appearance is quite characteristic for elastofibroma. (Right) Elastic van Gieson shows a classic pipe cleaner appearance with degenerated globules of elastic fibers in the background.



Elastic Staining of Elastic Fibers



TERMINOLOGY

Synonyms

- Elastofibroma dorsi

Definitions

- Ill-defined fibroelastic tumor-like condition comprised of enlarged and irregular elastic fibers

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Support for genetic predisposition (alterations of short arm of chromosome 1)
- Multifocality may suggest systemic enzymatic defect, resulting in abnormal elastogenesis
- Repeated trauma or friction unlikely

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon, reported in < 0.001% of soft tissue tumors
 - Preeleostofibroma-like reactions can be seen in autopsies (up to 24% of patients)
- Age
 - Elderly patients, nearly exclusively > 50 years old
 - Peak at 60-70 years
- Sex
 - Female > > male (5:1)
- Ethnicity
 - Increased frequency in Okinawa, Japan (but may be reporting bias)

Site

- Subscapular/infrascapular area, deep to muscle, sometimes attached to periosteum of ribs
- Between shoulder blades and lower neck
- Chest wall less common

Presentation

- Slow-growing, deep-seated, firm mass; frequently bilateral
- Uncommonly presents with pain or tenderness

Treatment

- Surgical approaches
 - Simple excision in symptomatic patients
 - Postoperative hematoma or seroma is frequent complication

Prognosis

- Excellent; isolated recurrences reported

IMAGING

MR Findings

- Inhomogeneous soft tissue mass with contrast enhancement

CT Findings

- Poorly circumscribed, heterogeneous soft tissue mass
- Signal intensity/attenuation similar to skeletal muscle with fat
- Frequently bilateral: Removes sarcoma from consideration

MACROSCOPIC

General Features

- Ill defined, nonencapsulated, rubbery, and firm
- White fibrous tissue with interposed yellow fat

Size

- Mean: 5 cm; range: up to 20 cm

MICROSCOPIC

Histologic Features

- Mixture of heavy dense bands of collagenous tissue dissected by fat and abnormal elastic fibers
 - Fat is generally entrapped
- Large numbers of elastic fibers
 - Elastic fibers are large (hypertrophic), coarse, thick, and darkly eosinophilic
 - Fragmented into linearly arranged globules, simulating beads on string or pipe cleaners
 - Globules have serrated edge
 - Degenerated elastic fibers create eosinophilic globules or balls in stroma

Fine-Needle Aspiration

- Cellular, braid-like, or fern leaf-like smears

Histochemistry

- Weigert or von Gieson elastic stains highlight bead-like arrangement

DIFFERENTIAL DIAGNOSIS

Spindle Cell Lipoma

- Spindle cells and adipose tissue but no degenerated collagen

Nuchal Fibroma

- Soft tissue at base of neck showing fat within fibrous connective tissue with entrapped nerves

Fibromatosis

- Heavily collagenized stroma with spindled fibroblasts arranged in single direction with parallel vessels

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Perineurioma

KEY FACTS

TERMINOLOGY

- Benign peripheral nerve sheath tumor, specifically of perineurial cell derivation that surrounds endoneurial connective tissue space of nerve fibers

CLINICAL ISSUES

- Wide age range: 2-85 years; mean: 45 years
- Superficial subcutaneous soft tissues of head and neck
- Local recurrence is uncommon (< 5% of cases)

MACROSCOPIC

- Usually discrete, solitary, well circumscribed, but without easily detected capsule
- Range: 0.3-20 cm; mean: ~ 3 cm

MICROSCOPIC

- Well circumscribed, focally showing changes suggesting collagenous capsule
- Spindled tumor cells organized in many patterns
- Fascicles, storiform or pinwheel

- Whorled to concentrically stratified
- Bipolar, bland, plump spindled cells with pale, eosinophilic long and thin cytoplasmic processes
- Nuclei vary: Oval, tapered, elongate, triangular, curved, or wavy with finely distributed chromatin
- Background stroma is collagenous, myxoid, or mixture
- Sclerosing, reticular (retiform), granular and epithelioid subtypes recognized

ANCILLARY TESTS

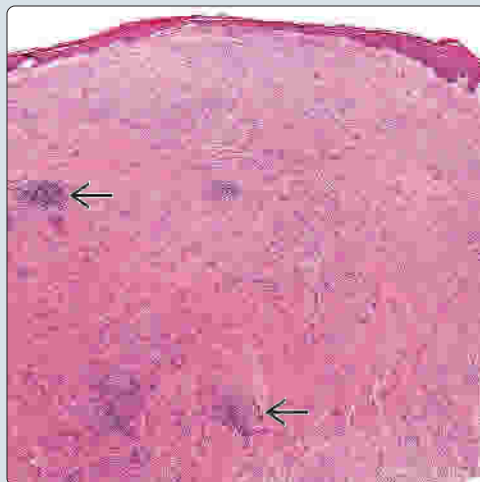
- EMA: Strong and diffuse
- Claudin-1: Distinctly particulate pattern along cell membrane
- GLUT1: Usually membranous to stippled

TOP DIFFERENTIAL DIAGNOSES

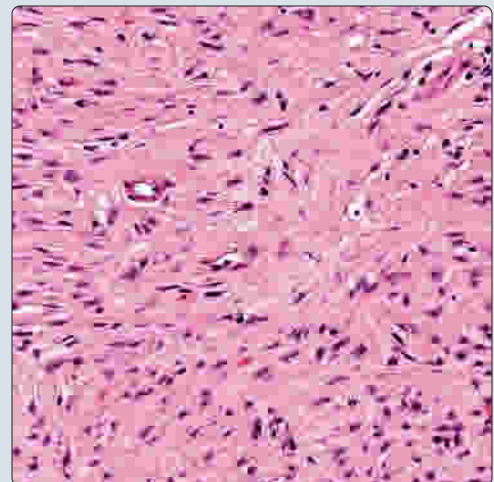
- Neurofibroma, schwannoma, solitary fibrous tumor, myoepithelioma, meningioma, desmoid fibromatosis

(Left) There is an intact surface epithelium overlying a proliferation of spindled cells arranged in a vaguely storiform pattern with focal small whorls. Collections of inflammatory cells are present. **(Right)** There is a haphazard spindle cell proliferation showing a syncytial appearance. The cells show slightly spindled nuclei with cytoplasmic processes. The background stroma is slightly loose to myxoid.

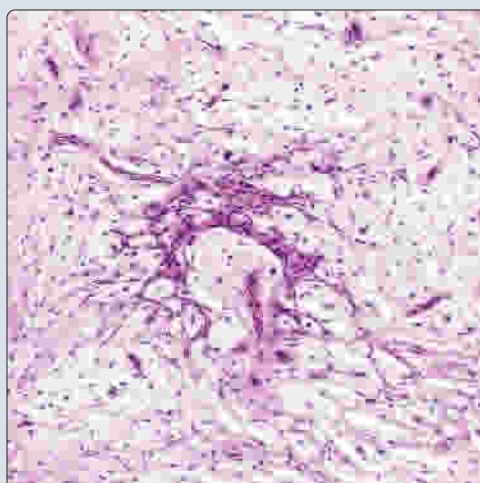
Submucosal Spindle Cell Proliferation



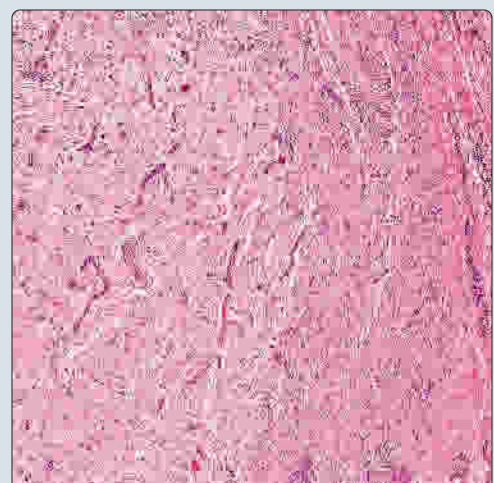
Syncytial Appearance to Spindled Cells



Epithelioid Cells in Sclerosing Perineurioma



Haphazard Storiform Proliferation



(Left) Epithelioid and spindle cells in trabecular or whorled pattern are shown within a background of myxoid to fibrotic stroma. **(Right)** The proliferation blends at the periphery with the densely collagenized stroma. There is a haphazard storiform appearance to the proliferation. The stroma is myxoid to edematous, perhaps having a vaguely tissue culture-like appearance.

TERMINOLOGY

Abbreviations

- Soft tissue perineurioma (STP)

Synonyms

- Sclerosing perineurioma

Definitions

- Benign peripheral nerve sheath tumor, specifically of perineurial cell derivation that surrounds endoneurial connective tissue space of nerve fibers
 - Tumors are traditionally separated into intraneural, sclerosing, and soft tissue perineurioma
 - Perineurial cells can be seen in other tumors, such as neurofibroma and schwannoma

ETIOLOGY/PATHOGENESIS

Pathogenesis

- May be related to Schwann cells, fibroblasts, or arachnoid cap cells

CLINICAL ISSUES

Epidemiology

- Incidence
 - Exceedingly rare
 - Represents < 0.5% of peripheral nerve sheath tumors
- Age
 - Wide range: 2-85 years; mean: 45 years
 - Majority: 2nd-5th decades
- Sex
 - Slight female predilection (for extraneural tumors)

Site

- Superficial subcutaneous soft tissues of head and neck
 - ~ 15% of all perineuriomas affect head and neck sites
 - May rarely affect gnathic bones (mandible)
- Oral cavity is affected about 4% of time

Presentation

- Most patients present with solitary painless mass
 - Sclerosing type usually affects superficial dermis
- May have syndrome/familial association
 - Neurofibromatosis type 2 (NF2): Only for intraneural type tumors
 - Nevoid basal cell carcinoma (Gorlin) syndrome
 - Interestingly, both have meningioma in common
 - Perineurium may be derived from arachnoid cap cells

Treatment

- Complete, wide excision to prevent recurrence

Prognosis

- Local recurrence is uncommon (< 5% of cases)
 - May develop late, and only if incompletely excised
- Pleomorphic cells and infiltrative margins do not affect clinical outcome

MACROSCOPIC

General Features

- Usually discrete, solitary, well circumscribed, but without easily detected capsule

Size

- Range: 0.3-20 cm; mean: ~ 3 cm

MICROSCOPIC

Histologic Features

- Superficial subcutaneous or dermal site
- Well circumscribed, focally showing changes suggesting collagenous capsule
 - Infiltrating borders can be seen, but not significant invasion
- Spindled tumor cells organized in many patterns
 - Fascicles, storiform or pinwheel
 - Whorled to concentrically stratified
 - Lamellar architecture
- Tumors are hypo- or hypercellular, with alternating zones
- Bipolar, bland, plump spindled cells with pale, eosinophilic long and thin cytoplasmic processes
- Nuclei vary: Oval, tapered, elongate, triangular, curved, compressed, twisted, or wavy with finely distributed chromatin
 - Intranuclear pseudoinclusions are rare
- Isolated pleomorphic cells (ancient change) are unusual
- Background stroma is collagenous, myxoid, or mixture
 - Sclerotic, round to elliptical collagen deposits may be present
 - Pericellular cracking or clefting between collagen and cells
- Mitoses are sparse to absent
- Degeneration and hemorrhage may be present
- Calcifications (calcospherites or metaplastic bone) are exceptional
- Chronic inflammation is uncommon
- Peripheral nerve association is unique, usually "twigs" of nerves
- Vessel hyalinization is not present
- Sclerosing, reticular (retiform), granular and epithelioid subtypes are recognized, although very rare in head and neck
 - Reticular: Lace-like growth pattern of anastomosing cords of spindle cells
 - Sclerosing: Epithelioid and spindle cells in trabecular or whorled pattern within markedly dense sclerotic stroma
 - Intraneural: Perineurial cells form concentric layers around nerve fibers (pseudo-onion bulb)

ANCILLARY TESTS

Cytology

- Cellular smears with sheets and clusters of spindle-shaped tumor cells
- Cells are bipolar with cytoplasmic extensions
- May have signet ring appearance
- Prominent myxoid background

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
EMA	Positive	Cytoplasmic	Strong and diffuse in all cases
Claudin-1	Positive	Cell membrane	Distinctly particulate pattern along cell membrane in nearly all cases
GLUT1-cytoplasm	Positive	Cell membrane	Usually membranous to stippled
CD34	Positive	Cytoplasmic	Seen in up to 65% of cases
Collagen IV	Positive	Stromal matrix	Strong membranous staining of cells
Actin-sm	Positive	Cytoplasmic	Up to 20% of cases
S100	Positive	Nuclear & cytoplasmic	Only in up to 5% of cases
CK-PAN	Negative		
GFAP	Negative		
NFP	Negative		Axons adjacent to tumor may be highlighted
Desmin	Negative		
TLE1	Equivocal	Nuclear	Present in normal perineurial cells

Immunohistochemistry

- Variably positive with perineurial markers
 - EMA: Strong and diffuse in all cases
 - Claudin-1: Distinctly particulate pattern along cell membrane in nearly all cases
 - GLUT1: Usually membranous to stippled
 - CD34: Up to 65% of tumors may be positive
 - May have smooth muscle actin (~ 20%) and S100 protein (~ 5%)
- Strong membranous staining with collagen IV

Genetic Testing

- Monosomy of chromosome 22 in conventional STP
- Chromosome 10 aberrations seen in sclerosing variants
 - Deletion of 10q; t(2;10)(p23;q24); monosomy 10

Electron Microscopy

- Long, thin, cytoplasmic processes with incomplete basal lamina (basement membrane) and pinocytotic vesicles, and well-formed tight junctions
- Axons absent

DIFFERENTIAL DIAGNOSIS

Neurofibroma and Schwannoma

- Benign peripheral nerve sheath tumors include neurofibromas, schwannomas, and perineuriomas
 - Hybrid combinations of schwannoma/neurofibroma and perineurioma are known
 - Show alternating layers of S100 protein and EMA (+) cells layered adjacent to one another
- Schwannoma are encapsulated tumors, which may be associated with nerve in many cases
- Perivascular hyalinization is usually found
- **Positive:** S100 protein, SOX10; CD34 in NF

Solitary Fibrous Tumor

- Cellular tumors with spindled cells, vascular pattern, and much more heavily collagenized stroma
- **Positive:** CD34, Bcl-2, STAT6; **negative:** S100 protein, SOX10

Myoepithelioma

- Epithelial neoplasm arranged in nests, cords, and clusters, sometimes with ductal differentiation, but usually spindled to plasmacytoid cells
- **Positive:** CK-PAN, CK7, S100 protein, p63, GFAP, SMA, MSA, calponin

Meningioma

- Central nervous system association is usual, but ectopic tumors may be seen
- Whorled architecture with psammoma bodies
- Lacks collagen IV immunoreactivity
- **Positive:** EMA
 - Perineurial and arachnoidal cells may be related

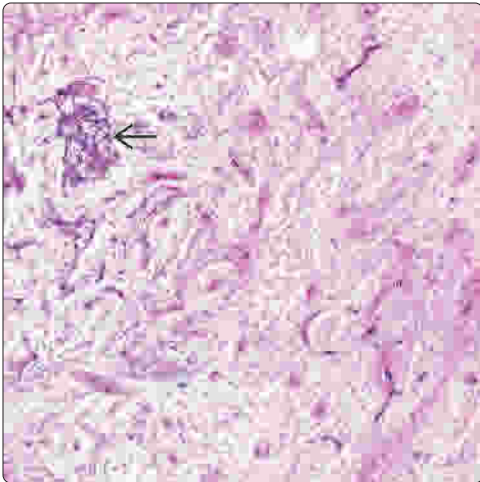
Desmoid Fibromatosis

- Ill-defined, infiltrative lesions with bland, purposefully directed spindled cells parallel to vessels
- **Positive:** Nuclear β -catenin

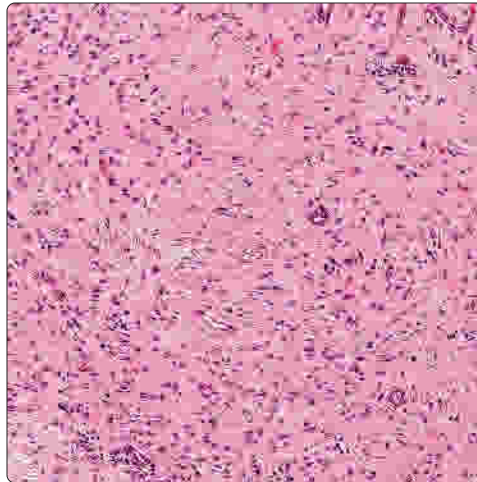
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Epithelioid Nests Within Stroma

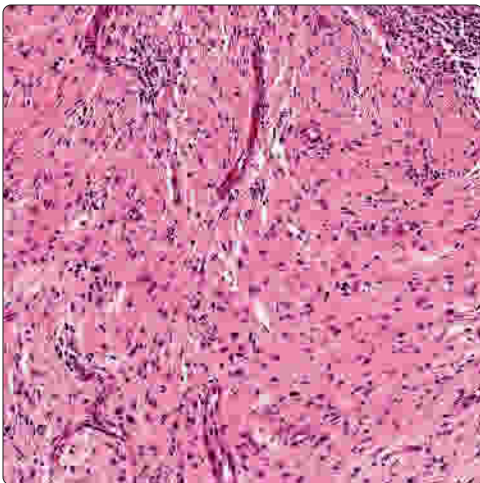


Syncytium of Spindled Cells

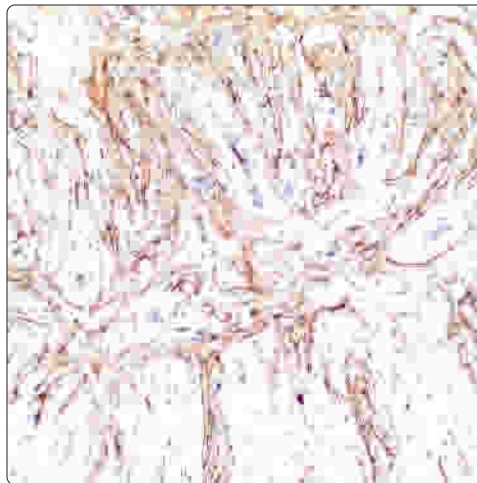


(Left) There is an epithelioid nest  set within an otherwise storiform to spindled cell population. **(Right)** The cells are arranged in a syncytial pattern, although the spindle cells are easily identified. There are vessels within the proliferation, but they do not show hyalinized walls.

Prominent Vessels in Perineurioma

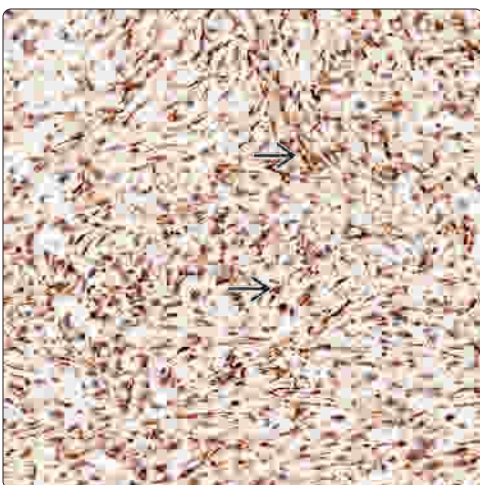


GLUT1 Highlights Spindled Cells

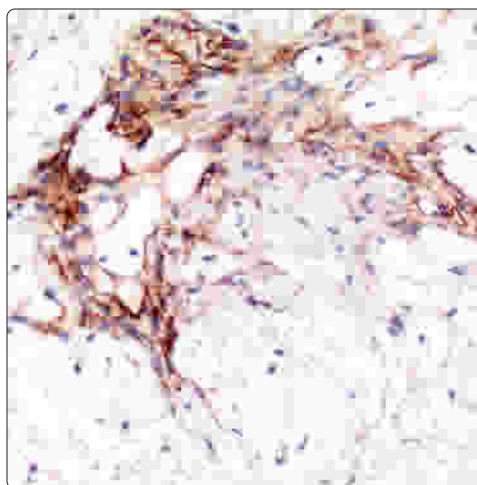



(Left) The proliferation is less cellular in this field, although the vessels are more prominent. There is still a lack of perivascular hyalinization. The nuclei are small and spindled. There is a lack of cytologic atypia and mitoses. **(Right)** The neoplastic spindle cells are highlighted by GLUT1, giving a slightly stippled to granular appearance. The wisps of cytoplasm are stained, creating a feathery appearance to the cells.

Claudin-1: Perineural Marker



EMA Stains Epithelioid Cells



(Left) Claudin-1 will frequently display a stippled, beaded, or granular staining , while also highlighting the cell membranes. This staining pattern is quite unique to this tumor. **(Right)** The cell membranes and cytoplasm show a variably strong reaction in the cells of a perineurioma. However, it is important to know the staining can be quite weak.

Lipoma

KEY FACTS

TERMINOLOGY

- Lipoma: Benign tumor of mature white fat
- Angiolipoma: Benign tumor of mature white fat cells with intermixed thin-walled vessels, often with thrombi
- Myolipoma (Lipomyoma): Benign tumor of mature fat and mature smooth muscle

CLINICAL ISSUES

- Common tumor but relatively uncommon in head and neck
- Soft tissue mass
- Gradual increase in size
- Soft tissue mass with slow size increase
- Multiple tumors in 5-15% (familial)
- Angiolipomas: Distinctive for pain and tenderness
- Treatment: Complete surgical excision
- Prognosis: Excellent overall

MACROSCOPIC

- Yellow, greasy cut surface

- Angiolipoma: Yellow pink
- Myolipoma: Intermixed with firm white-tan tissue

MICROSCOPIC

- Lipoma
 - Lobules of mature fat
 - Similar to normal fat with slight variation in size
- Angiolipoma
 - Capillaries of varying sizes with fibrin thrombi
- Myolipoma
 - Smooth muscle evenly distributed or in short fascicles

ANCILLARY TESTS

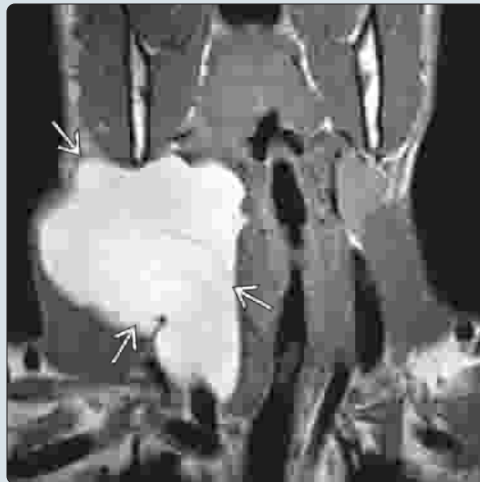
- Cytology: Fatty/lipid droplets on slides
 - Lobules of benign fibroadipose connective tissue

TOP DIFFERENTIAL DIAGNOSES

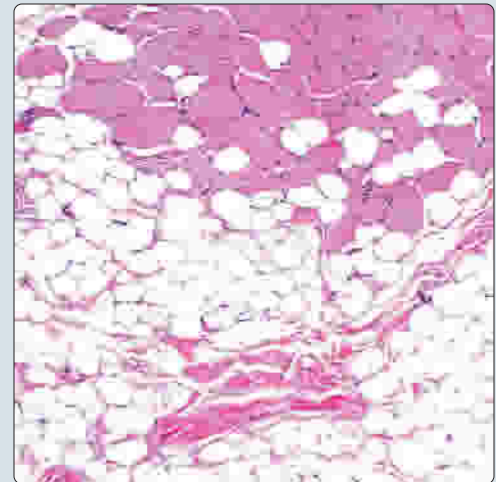
- Atypical lipomatous tumor/well-differentiated liposarcoma
- PEComa (Angiomyolipoma)

MR: Large Neck Lipoma

(Left) Coronal T1WI MR in a patient with a neck lipoma illustrates the craniocaudal extent of the mass. Scan also shows mass effect on the larynx, which was deviated across the midline, raising concern for liposarcoma rather than lipoma. Resection of the mass showed mature adipose tissue of benign lipoma. (Right) Intramuscular lipomas show varying levels of infiltration into the surrounding muscle.

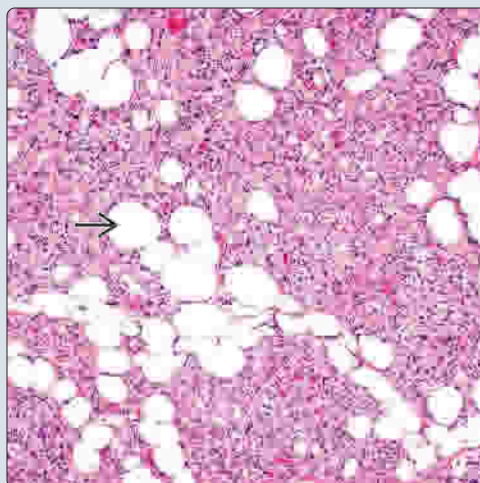


Intramuscular Lipoma

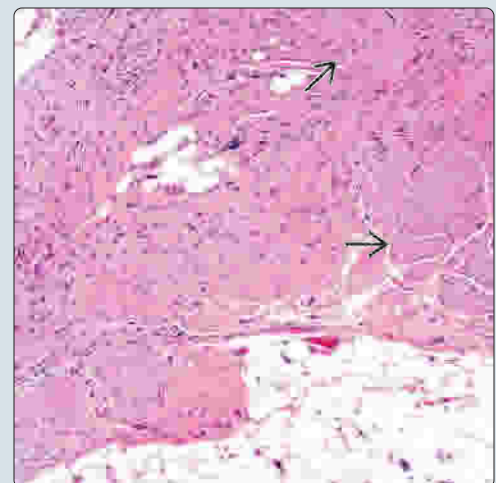


Angiolipoma

(Left) This example of an angiolipoma shows the characteristic mature fat cells admixed with small vessels. Fibrin thrombi can be readily seen in the vessels. Grossly, an angiolipoma will generally appear yellow-pink, oftentimes accompanied by a clinical history of tenderness. (Right) This example of myolipoma shows fat immediately associated with bundles of smooth muscle. The term myolipoma or lipomyoma is used for this lesion.



Myofibroma



TERMINOLOGY

Definitions

- Lipoma: Benign tumor of mature white fat
- Angiolipoma: Benign tumor of mature white fat cells with intermixed thin-walled vessels, often with thrombi
- Myolipoma (lipomyoma): Benign tumor of mature fat and mature smooth muscle

CLINICAL ISSUES

Epidemiology

- Incidence
 - Common tumor, but relatively uncommon in head and neck
 - Myolipomas are extremely rare
- Age
 - Wide age range
 - Angiolipomas: Young adults and teenagers
- Sex
 - Equal gender distribution
 - Variant tumors have male predominance

Site

- Head and neck is not common primary site
 - Posterior cervical space
 - Submandibular space
 - Anterior cervical space and parotid gland
 - Scalp and forehead

Presentation

- Soft tissue mass with slow size increase
- Multiple tumors in 5-15% (familial)
- Angiolipomas: Distinctive for pain and tenderness

Treatment

- Complete surgical excision

Prognosis

- Excellent overall prognosis
- Infiltrative lipomas are more likely to recur
- Rare complications related to anatomic site

IMAGING

Radiographic Findings

- Well-circumscribed, homogeneous mass clearly demonstrated on CT or MR
- Thin capsule, with smooth, noninvasive, convex margins
- Majority have homogeneous fat content
 - Thin septa may be seen

MACROSCOPIC

General Features

- Generally appear encapsulated or well circumscribed
- Yellow, greasy cut surface
- Angiolipoma: Yellow pink
- Myolipoma: Intermixed with firm white-tan tissue

Size

- Wide range: 0.5-30 cm

MICROSCOPIC

Histologic Features

- **Lipoma**
 - Lobules of mature fat, similar to normal fat, with slight size variation
 - Occasionally other types of tissue may be seen
 - Bone: Osteolipoma; cartilage: Chondrolipoma; fibrous tissue: Fibrolipoma
 - Intramuscular: May show infiltration
- **Angiolipoma**
 - Mature fat cells; fibrous changes in older lesions
 - Capillaries of varying sizes with fibrin thrombi
- **Myolipoma**
 - Mature fat cells with sclerosis and focal inflammation
 - Smooth muscle: Evenly distributed or short fascicles

ANCILLARY TESTS

Cytology

- Fatty/lipid droplets on slides
- Lobules of benign fibroadipose connective tissue

Immunohistochemistry

- Lipoma: S100 protein, vimentin positive
- Myolipoma: SMA, desmin positive smooth muscle cells

DIFFERENTIAL DIAGNOSIS

For Lipoma

- Atypical lipomatous tumor/well-differentiated liposarcoma)
 - Variable cell size, irregular hyperchromatic nuclei, lipoblasts
 - MDM2 & CDK4+ (FISH more sensitive than IHC)
- Spindle cell lipoma
 - Distinctive fibrous connective tissue, collagen and fat; fibrin thrombi; CD34+
- Lipoblastoma
 - Affects primarily children, lobulated, thicker fibrous septa, lipoblasts
- Lipomatosis
 - Associated with genetic disorders; diffuse growth of fat tissue, possibly infiltrating other tissues

For Myolipoma

- Leiomyoma and leiomyosarcoma: Lacks fat
- Perivascular epithelioid cell tumors (PEComa) include angiomyolipoma
 - Smooth muscle and fat tumors, with distinctive epithelioid appearance; **positive**: HMB45, SMA

For Angiolipoma

- Hemangioma: Vessels only, variable size
- Kaposi sarcoma: Infiltrative, cellular, eosinophilic globules
- Angiosarcoma: Infiltrative, necrosis, pleomorphism

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Spindle Cell Lipoma

KEY FACTS

TERMINOLOGY

- Distinctive lipomatous tumor composed of admixture of bland spindled cells, hyperchromatic rounded cells, and multinucleated giant cells associated with ropey collagen

CLINICAL ISSUES

- Lipoma: Spindle cell lipoma (60:1)
- Age
 - Mean: 55 years; range: 40-70 years
- Male >> female (9:1)
- Subcutaneous fat of posterior neck, upper back, shoulder girdle
- Usually asymptomatic, painless mass, often present for years

MACROSCOPIC

- Well-circumscribed, firm to myxoid, pale yellow/white ovoid mass

MICROSCOPIC

- Mixture of mature adipocytes, bland fibroblast-like spindle cells and ropey collagen
- Matrix with variable amounts of birefringent collagen fibers and mucosubstances
- Mast cells easily identified
- Absent mitoses
- Pleomorphic lipoma
 - Hyperchromatic, multinucleated cells, with nuclei arranged in floret pattern


ANCILLARY TESTS

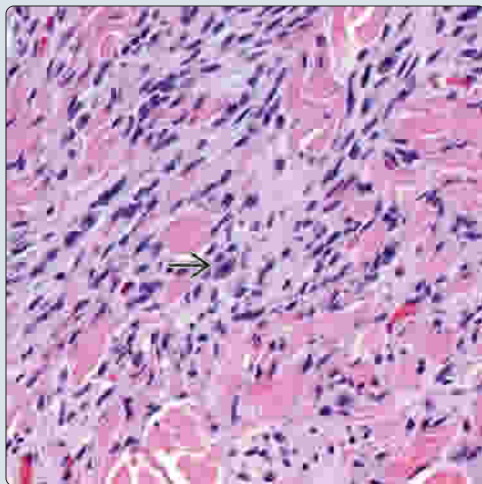
- Positive: CD34 (spindle cells); S100 protein (weak &/or focal)

TOP DIFFERENTIAL DIAGNOSES

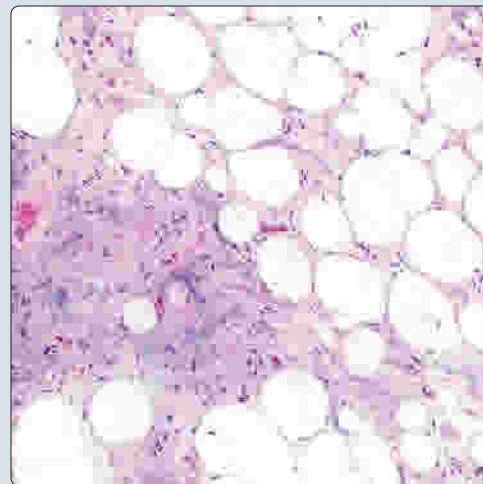
- Well-differentiated liposarcoma, peripheral nerve sheath tumor, lipoma and other lipoma variants, myxoma, solitary fibrous tumors, dermatofibrosarcoma protuberans

Spindle Cell Proliferation and Collagen



(Left) There is a well-developed spindled cell population associated with keloid-like collagen deposition in this example of a spindle cell lipoma. There is no fat in this field. A mast cell  is noted. (Right) Spindle cell lipoma may be associated with a myxoid change of the stroma. Lipocytes are easily identified in this field.

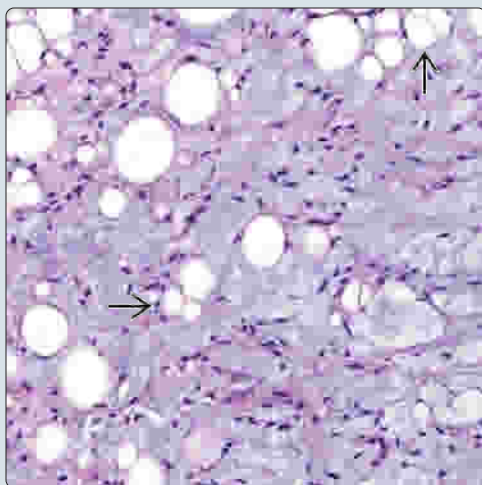


Myxoid Change in Spindle Cell Lipoma

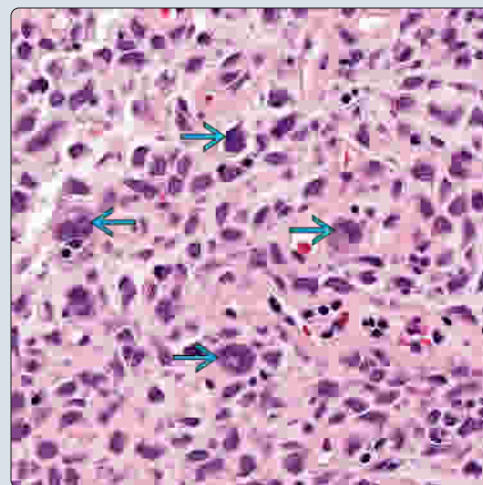


Myxoid Change With Pseudolipoblasts

(Left) There are many lipocytes in this field, some of which have a compressed nucleus out to the periphery and multiple vacuoles, creating pseudolipoblasts . There is a prominent myxoid change in this tumor. (Right) This field shows a number of profoundly pleomorphic nuclei, including multinucleated cells . The pleomorphism is considered an ancient change.



Pleomorphic Lipoma With Ancient Change



TERMINOLOGY

Abbreviations

- Spindle cell lipoma (SCL)

Definitions

- Distinctive lipomatous tumor composed of admixture of bland spindled cells, hyperchromatic rounded cells, and multinucleated giant cells associated with ropey collagen

CLINICAL ISSUES

Epidemiology

- Incidence
 - 1.5% of all adipocytic neoplasms
 - Lipoma: SCL (60:1)
- Age
 - Mean: 55 years; range: 40-70 years
- Sex
 - Male > > female (9:1)

Site

- Subcutaneous fat of posterior neck, upper back, shoulder girdle
- Less common: Face, parotid gland, oral cavity (lip, tongue)

Presentation

- Usually asymptomatic, painless mass, often present for years
- Familial and multifocal cases are exceptional

Treatment

- Local excision; no radical procedures required

Prognosis

- Excellent, with local recurrence only rarely reported

MACROSCOPIC

General Features

- Well-circumscribed, firm to myxoid, pale yellow/white ovoid mass

Size

- Mean: 5 cm; range: 0.5-12 cm

MICROSCOPIC

Histologic Features

- Develops within fat (subcutaneous, oral or salivary gland)
- Mixture of mature adipocytes, bland fibroblast-like spindle cells and ropey collagen
 - Fibroblastic-like cells often arranged in parallel array
- Matrix with variable amounts of birefringent collagen fibers and mucosubstances
 - Myxoid type material
- Mast cells easily identified
- Profound, usually focal, nuclear pleomorphism
 - Considered ancient, retrogressive, or degenerative change
- Absent mitoses
- Secondary changes can be seen
 - Fat necrosis, atrophy, hyalinization

Pleomorphic Lipoma

- Spectrum of same tumor
- Hyperchromatic, multinucleated cells, with nuclei arranged in floret pattern
- Lipoblasts may be present

Fat-Free and Fat-Poor Variants

- Spindle cell proliferation predominates without or sparse adipocytes

ANCILLARY TESTS

Cytology

- Mixture of mature adipocytes, monotonous spindle cells, and collagen fibers in varying proportions
- Myxoid matrix and mast cells are seen

Immunohistochemistry

- **Positive:** CD34 (spindle cells); S100 protein (weak &/or focal)

Genetic Testing

- Loss from the region 16q13-qter
- 13q deletion: 13q12 and 13q14-q22

DIFFERENTIAL DIAGNOSIS

Well-Differentiated Liposarcoma

- Lipoblasts, chicken wire vascular pattern, myxoid change

Peripheral Nerve Sheath Tumors

- Antoni A areas with buckled nuclei and Verocay bodies; **Positive:** S100 protein, SOX10

Chondroid Lipoma

- Chondroid material without spindle cells or collagen

Myxoma

- No fat or thick bundles of collagen; hypocellular tumor

Solitary Fibrous Tumor

- Spindled population with keloid-like collagen deposition and dilated vascular pattern
- **Positive:** CD34, STAT6, bcl-2; **negative:** S100 protein, SOX10

Dermatofibrosarcoma Protuberans

- Usually in young patients; storiform spindled cells infiltrating subcutaneous fat; CD34(+)

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Lipoblastoma

KEY FACTS

TERMINOLOGY

- Rare, benign tumor arising from embryonic white fat

CLINICAL ISSUES

- Infancy and childhood
- Male > female (2:1)
- Rapidly enlarging, painless mass
- Treatment: Complete excision, preserving vital structures
- Prognosis: Excellent long-term outcome
- Recurrences common (~ 30%)
- Neck is uncommon site
 - ~ 8% of tumors develop in head and neck
- Most common locations (order of frequency)
 - Extremities > axilla > mediastinum > retroperitoneum > prevertebral

MACROSCOPIC

- Encapsulated
- Lobulated with fibrous bands

- White to yellow cut surface

MICROSCOPIC




- Lobulated adipose tissue with fibrous septa
- Mixture of mature fat cells and lipoblasts
- Stroma may be focally myxoid

ANCILLARY TESTS

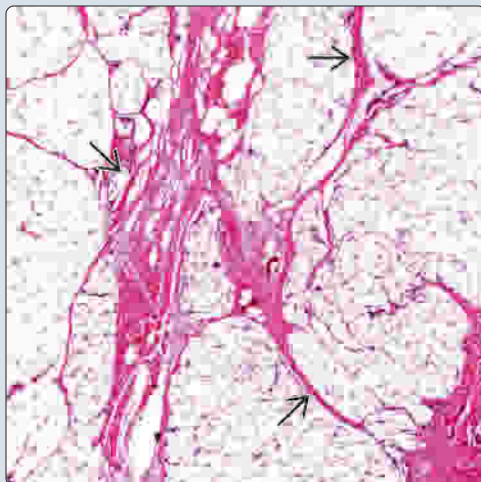
- Rearrangements involving *PLAG1* gene (8q12.1)
 - Fusion proteins (*HAS2-PLAG1* or *COL1A2-PLAG1*) encode for *PLAG1* protein

TOP DIFFERENTIAL DIAGNOSES

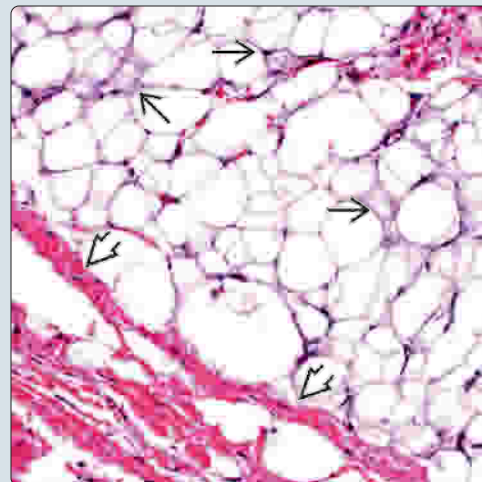
- Lipoblastomatosis
- Myxoid liposarcoma
- Hibernoma
- Lipoma/fibrolipoma/angioliipoma



(Left) This low-power image shows the characteristic lobulated appearance of a lipoblastoma. The connective tissue septa  separates the lobules, which are made up of mature adipose cells and lipoblasts. **(Right)** Hematoxylin and eosin stain shows an admixture of multivacuolated lipoblasts  and mature adipose cells abutting a fibrous connective tissue septum . No mitotic figures are seen and should be very rare.

Connective Tissue Septa

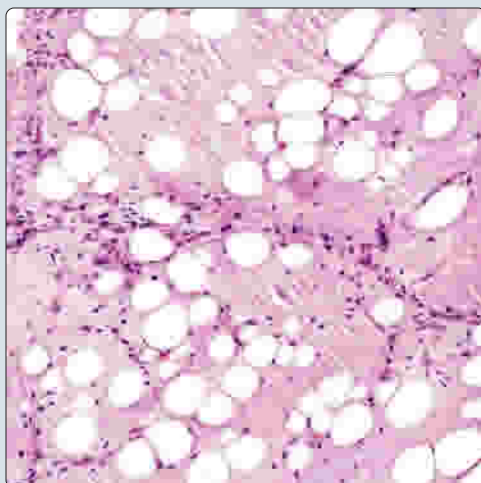


Lipoblasts and Mature Adipose Cells

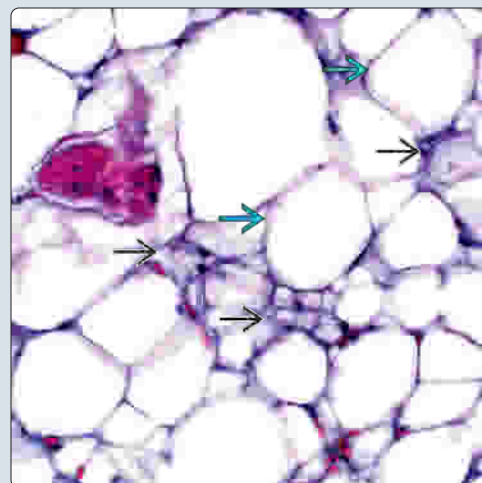


(Left) This tumor was identified in a 18-month-old boy. The majority of the tumor showed this myxoid stroma closely associated with mature adipose cells and lipoblasts. Two years after surgical excision, there is no reported recurrence. **(Right)** High-power image shows a lipoblastoma with mature fat cells  and characteristic multivacuolated lipoblasts . There is compression of the nucleus by the fat.

Myxoid Stroma



Multivacuolated Lipoblasts



TERMINOLOGY

Definitions

- Benign tumor derived from embryonic white fat

CLINICAL ISSUES

Epidemiology

- Incidence
 - Exceedingly rare
- Age
 - Infancy and childhood
 - Mean: 2 years; range: Up to 12 years
- Sex
 - Male > female (2:1)

Site

- Neck is uncommon site
 - ~ 8% of tumors develop in head and neck
- Most common locations (order of frequency)
 - Extremities > axilla > mediastinum > retroperitoneum > prevertebral

Presentation

- Rapidly enlarging, painless mass (~ 50%)
- Compression of adjacent nerves or cervical structures
 - Respiratory distress, dysphagia, odynophagia
 - Trismus, hoarseness, or respiratory compromise
 - Horner syndrome: Drooping eyelid, decrease in pupil size, decrease in sweating on affected side
 - Hemiparesis

Treatment

- Complete excision to preserve vital structures

Prognosis

- Excellent long-term outcome
- Recurrences common (~ 30%)
 - Associated with incomplete excision

IMAGING

Ultrasonographic Findings

- Shows solid, noncystic mass

MR Findings

- Well-circumscribed, heterogeneous mass
 - T1WI: Predominately high signal but shows lower intensity than mature fat
 - T2WI: Predominately high signal, caused by lipoblasts and myxoid stroma

MACROSCOPIC

General Features

- Encapsulated
- Lobulated with fibrous bands
- White to yellow cut surface

Size

- Range: 1.2-15.5 cm

MICROSCOPIC

Histologic Features

- Lobulated adipose tissue
- Fibrous septa
- Entrapment of skeletal muscle fibers
- Mixture of mature fat cells and lipoblasts
 - Mature cells tend to be located centrally
 - Lipoblasts may be multivacuolated
 - Lipoblasts appear to be in various stages of differentiation
- Stroma may be focally myxoid
 - Stellate to spindled mesenchymal cells
- Rare mitoses (< 1/20 HPF)

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** S100 protein, CD34

Genetic Testing

- Rearrangements involving chromosome 8q11-q13 region
 - *PLAG1* gene (8q12.1)
 - Part of subfamily of C2H2 zinc finger transcription factors that activate transcription
 - Rearrangements cause promoter-swapping event, with other genes' promoters causing *PLAG1* transcriptional up-regulation
 - Fusion proteins (*HAS2-PLAG1* or *COL1A2-PLAG1*) encode for *PLAG1* protein
- Metaphase or interphase FISH using *PLAG1* probes
- Gain of chromosome 8 in many cases

DIFFERENTIAL DIAGNOSIS

Lipoblastomatosis

- Unencapsulated
- Diffuse growth
- Infiltrative into surrounding tissue

Myxoid Liposarcoma

- Occurs primarily in 3rd-6th decades
- Atypical lipoblasts
- Mitosis
- Mature adipose cells seen peripherally
- Characterized by t(12;16)(q13;p11)

Lipoma/Fibrolipoma/Angiolipoma

- Lack lipoblasts

Hibernoma

- Fat cells have eosinophilic, granular cytoplasm
- Rearrangement in chromosome 11q13

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Nuchal-Type Fibroma

KEY FACTS

TERMINOLOGY

- Nuchal-type fibroma (NTF)
 - Benign, hyalinized, fibroblastic proliferation involving dermis and subcutis

CLINICAL ISSUES

- Rare
- Male > female
- Wide age range; peak: 3rd-5th decades
- Most common in posterior neck
- Long history of superficial mass
- Treatment: Excision
- Excellent outcome, without functional compromise
- Due to frequent recurrences, follow-up is indicated

MACROSCOPIC

- Poorly circumscribed and unencapsulated
- Firm, white
- May extend into deep dermis or skeletal muscle

- Size range: Up to 8 cm; mean: 3.5 cm

MICROSCOPIC



- Thick, haphazardly arranged collagen fibers
- Unencapsulated with low cellularity
- Entrapped mature adipose tissue and skeletal muscle
- Proliferation of peripheral nerves, usually deep within collagen fibers
- May see scattered lymphocytes

ANCILLARY TESTS

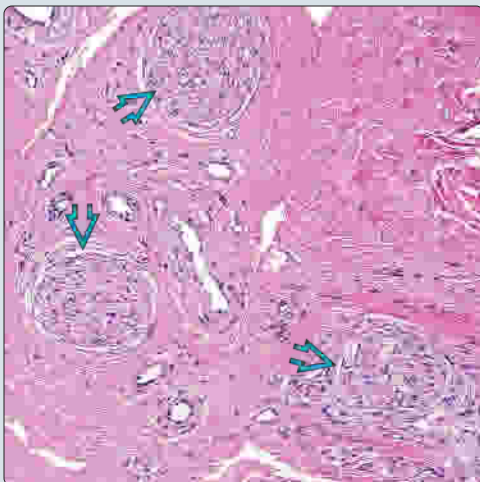
- **Positive:** Vimentin, CD34, nuclear β -catenin

TOP DIFFERENTIAL DIAGNOSES

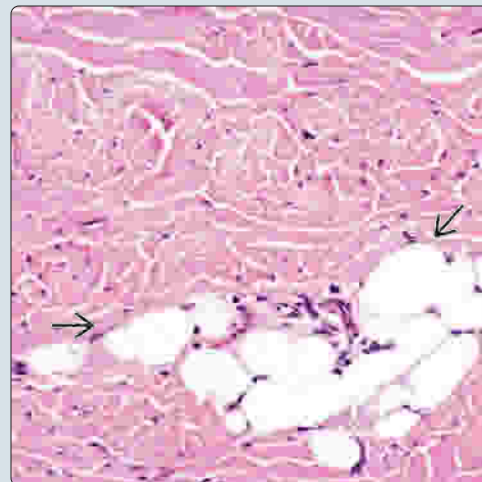
- Elastofibroma
- Fibrolipoma
- Desmoid-type fibromatoses
- Nuchal fibrocartilaginous pseudotumor
- Scar



(Left) Hematoxylin and eosin shows entrapped nerves , a feature of nuchal-type fibromas. This particular tumor was asymptomatic but was reportedly present for 2-3 years. **(Right)** A nuchal-type fibroma of the posterior neck shows the entrapment of mature adipose tissue  in the dense, haphazardly arranged collagen.

Entrapped Nerves in Nuchal-Type Fibroma

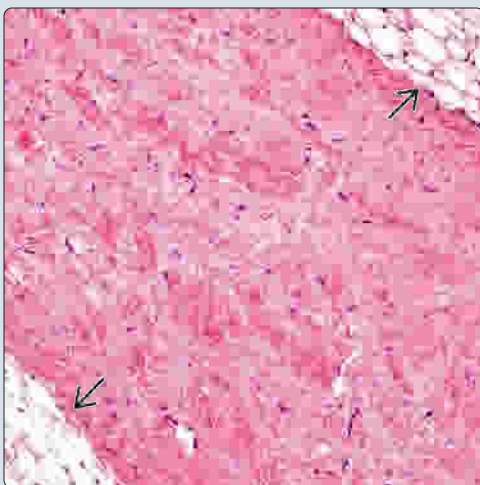


Entrapped Mature Fat



(Left) Hematoxylin and eosin shows a nuchal-type fibroma with thick, haphazardly arranged collagen fibers. Entrapment of mature adipose tissue  is readily identified. Due to frequent recurrences, clinical follow-up is recommended. **(Right)** Hematoxylin and eosin shows thick collagen bundles . These bundles may intersect to create a lobular architecture. This lesion was encapsulated and ill defined.

Fat Entrapment With Haphazard Collagen



Thick Collagen Bundles



TERMINOLOGY

Abbreviations

- Nuchal-type fibroma (NTF)

Synonyms

- Nuchal fibroma
 - Terminology no longer technically correct since lesions may rarely be found in areas other than posterior neck

Definitions

- Benign, hyalinized, fibroblastic proliferation involving dermis and subcutis

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Unknown; may be related to local or systemic factors

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare
- Age
 - Wide range; peak: 3rd-5th decades
- Sex
 - Male > female
 - Syndrome-associated, equal gender distribution

Site

- Most common location is posterior neck
- Other sites may be affected

Presentation

- Generally asymptomatic
- Long history of superficial mass; solitary lesion
- Strong association with diabetes mellitus and Gardner syndrome

Treatment

- Excision is treatment of choice
- In patients with Gardner syndrome, up to 45% will develop desmoid-type fibromatosis at other sites

Prognosis

- Excellent outcome, without functional compromise
- Due to frequent recurrences, follow-up is indicated

MACROSCOPIC

General Features

- Poorly circumscribed and unencapsulated, firm, white
- May extend into deep dermis or skeletal muscle

Size

- Range: Up to 8 cm
- Mean: 3.5 cm

MICROSCOPIC

Histologic Features

- Unencapsulated and ill defined
- Thick, haphazardly arranged collagen fibers

- Low cellularity, overall bland appearance
- Vague lobular pattern
- Entrapped
 - Mature adipose tissue within collagen bundles
 - Proliferation of peripheral nerves
 - Similar to traumatic neuroma, with perineural fibrosis
 - Skeletal muscle
 - Scattered lymphocytes
 - May see encasement of adnexa from associated skin
- Elastic fibers may occasionally be altered

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** Vimentin, CD34, CD99 (a few cases)
 - Nuclear β -catenin (up to 2/3 of cases)
- **Negative:** Desmin, actins
- CD34 highlights vessels

DIFFERENTIAL DIAGNOSIS

Elastofibroma

- Abundant and abnormal elastic fibers, often hypertrophic
- Fragmented and degenerated fibers create lobules or balls in stroma

Fibrolipoma

- Well circumscribed and encapsulated with much more adipose tissue
- Lacks entrapped nerves

Desmoid-Type Fibromatoses

- More cellular, but not in subcutaneous tissues, showing parallel fiber distribution
- Can demonstrate aggressive behavior

Nuchal Fibrocartilaginous Pseudotumor

- Deep to fascia, at base of skull
- Cartilaginous metaplasia

Lipomatosis

- Sheets of adipocytes infiltrating skeletal muscle and other tissues
- Associated with numerous systemic diseases

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Should exclude Gardner syndrome

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4. Samadi DS et al: Nuchal fibroma: a clinicopathological review. Ann Otol Rhinol Laryngol. 109(1):52-5, 2000
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KEY FACTS

TERMINOLOGY

- Benign neoplasm of vestigial brown fat

CLINICAL ISSUES

- Adults most frequently
- Patients usually younger than patients with lipoma
- Slight male predominance
- Head and neck: Shoulders, neck, scapular
- Slow-growing painless solitary mass

IMAGING

- Well-defined, heterogeneous mass
- PET: May show abnormally intense FDG hyperfixation

MICROSCOPIC

- Wide range: 1-27 cm, mean: 10 cm
- Uniform, round to oval or polygonal cells
- Granular eosinophilic cells with prominent borders
- Coarsely multivacuolated fat cells (pale cells)

- Cells with large cytoplasmic lipid droplets interspersed
- Centrally placed small nuclei lacking atypia
- Background of rich vascularity
- **Variants:** Myxoid, lipoma-like, spindle cell

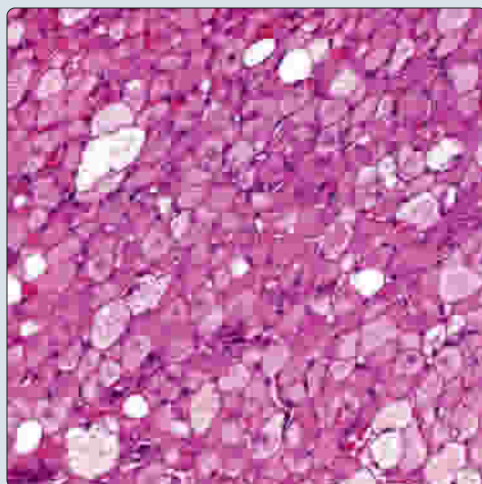
ANCILLARY TESTS

- Oil red O(+) droplets of cytoplasmic lipid
- **Positive**
 - S100 protein and CD31 (membrane and vacuoles)
 - AP2 protein strongly (but also positive in lipoblasts)
 - Multilocular cells express uncoupling protein 1 (UCP1), unique brown fat mitochondrial protein
- Structural rearrangements of 11q13-21

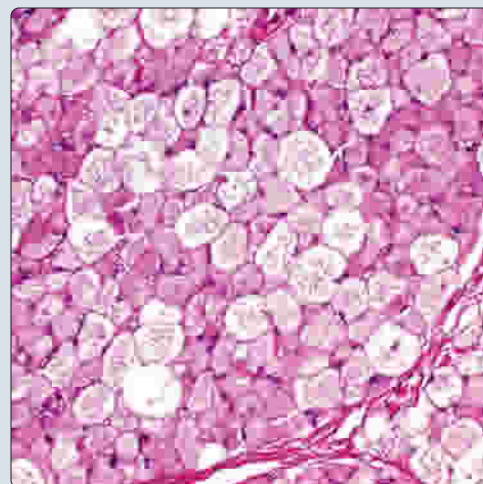
TOP DIFFERENTIAL DIAGNOSES

- Adult rhabdomyoma
- Granular cell tumor
- Liposarcoma
- Lipoblastoma

Sheets of Polygonal Brown Fat Cells

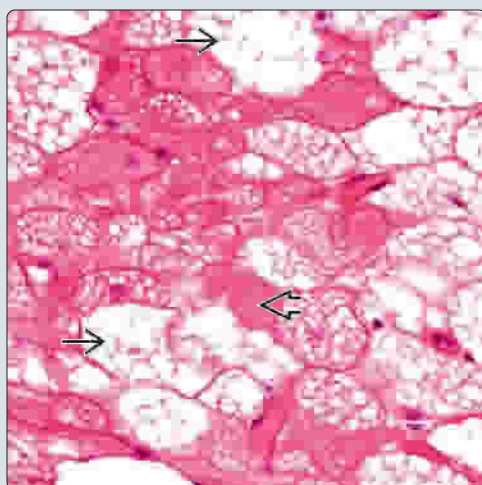


Microvacuolation of Hibernoma Cells

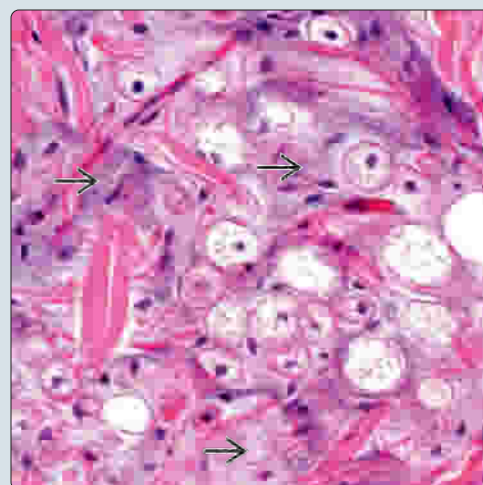


(Left) There are sheets of large, polygonal cells that comprise this hibernoma. There are microvesicular cells as well as cell with more compact, eosinophilic to granular cytoplasm. (Right) High-power H&E shows microvacuolation of many of the cells but a more solid and granular appearance in others.

Cytoplasmic Vacuoles of Variable Size



Myxoid Variant of Hibernoma



(Left) This hibernoma shows a much more prominent cytoplasmic vacuole formation. Single large vacuoles within cells are juxtaposed to microvacuolated cells. Isolated granular cells are present. (Right) The myxoid variant has myxoid change in the stroma immediately surrounding the granular microvesicular cells. Fat is also present in the background.

TERMINOLOGY**Synonyms**

- Fetal lipoma; lipoma of embryonic fat

Definitions

- Benign neoplasm of vestigial brown fat

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Rare
- Age
 - Adults most frequently (mean: 4th decade)
 - Patients usually younger than patients with lipoma
- Sex
 - Slight male predominance

Site

- Head and neck: Shoulders, neck, scapular

Presentation

- Slow-growing painless solitary mass, often for years
- Subcutis most frequently; rarely intramuscular

Treatment

- Complete surgical excision

Prognosis

- Excellent without aggressive behavior
 - Rare recurrence (only when incompletely excised)

IMAGING**General Features**

- Well-defined, heterogeneous mass
- MR T1WI show mass, which is diffusely although only slightly hypointense to subcutaneous fat
- PET: May show abnormally intense FDG uptake

MACROSCOPIC**General Features**

- Well-defined, encapsulated or circumscribed tumors
- Soft, yellow, tan to deep brown-red

Size

- Wide range: 1-27 cm; mean: 10 cm

MICROSCOPIC**Histologic Features**

- Mass resembling brown adipose tissue
- While 4 histologic types are recognized, 1 is most common (typical)
- Background of rich vascularity
- **Lobular type**
 - Variable degrees of differentiation
 - Uniform, round to oval cells
 - Granular eosinophilic cells with prominent borders
 - Coarsely multivacuolated fat cells (pale cells)
 - Centrally placed small nuclei lacking atypia
 - Cells with large cytoplasmic lipid droplets interspersed

Variants

- **Myxoid variant**
 - Loose, basophilic matrix, thick fibrous septa, foamy histiocytes
- **Lipoma-like variant**
 - Univacuolated lipocytes, with only isolated hibernoma cells
- **Spindle cell variant**
 - Spindle cell lipoma combined with hibernoma; neck or scalp affected; CD34(+)

ANCILLARY TESTS**Cytology**

- Smears of small, round, brown fat-like cells
 - Uniform, small cytoplasmic vacuoles; round, small nuclei
- Small, branching capillaries
- Mature fat cells are also present

Histochemistry

- Oil red O(+) droplets of cytoplasmic lipid

Immunohistochemistry

- **Positive**
 - S100 protein (~ 80%)
 - AP2 protein strongly (but also positive in lipoblasts)
 - CD31 intensely and diffusely: Membrane and vacuoles
 - Multilocular cells express uncoupling protein 1 (UCP1), unique brown fat mitochondrial protein

Genetic Testing

- Structural rearrangements of 11q13-21 most characteristic
 - *MEN1* gene (11q13.1) is most frequently deleted

DIFFERENTIAL DIAGNOSIS**Adult Rhabdomyoma**

- Polygonal cells, with granular not vesicular cytoplasm showing cross striation, spiderweb cells and crystals
- Large amounts of glycogen

Granular Cell Tumor

- Eosinophilic, granular cytoplasm, with round nuclei, often with nerve association
- **Positive:** S100 protein, SOX10, CD68

Liposarcoma

- True lipoblasts: Nuclear notches and pleomorphism, with different stroma and vascularity

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3. Bancroft LW et al: Benign fatty tumors: classification, clinical course, imaging appearance, and treatment. *Skeletal Radiol.* 35(10):719-33, 2006
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6. Furlong MA et al: The morphologic spectrum of hibernoma: a clinicopathologic study of 170 cases. *Am J Surg Pathol.* 25(6):809-14, 2001
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KEY FACTS

TERMINOLOGY

- Cystic hygroma
- Malformation of lymphatic system, generally considered congenital

ETIOLOGY/PATHOGENESIS

- Associated with genetic syndromes, including Turner syndrome, Noonan syndrome, Maffucci syndrome, trisomies 13, 18, 21

CLINICAL ISSUES

- Often present at birth
- Usually (~ 90%) diagnosed in first 2 years of life
- Most common in posterior triangle > anterior triangle (more symptoms)
- Treatment
 - Complete resection (treatment of choice)
 - Intralesional injections of sclerosing agents

IMAGING

- Ultrasound: Cystic lesion with homogenous cavities
- CT: Nonenhancing, multiple homogeneous cavities

MICROSCOPIC

- Variably sized lymphatic spaces lined by endothelial cells
- Lumina contain
 - Lymph, lymphocytes, and erythrocytes
- Large vessels may have smooth muscle layers
- Longstanding lesions may show fibrosis and inflammation

ANCILLARY TESTS

- **Positive:** FVIIIIRAg, CD31, CD34, D2-40 (podoplanin)

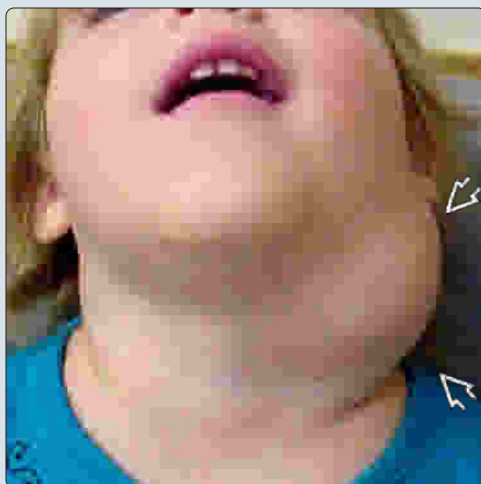
TOP DIFFERENTIAL DIAGNOSES

- Hemangioma, metastatic tumor, lymphangiectasia, Kaposi sarcoma

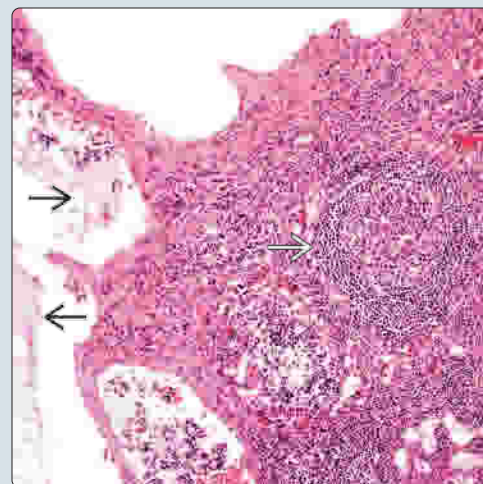
Lateral Neck Lymphangioma

(Left) The large, soft, ballotable left neck mass in this young girl proved to be a lymphangioma. The recurrence rate of such a lesion is especially high.

(Right) This hematoxylin and eosin, medium-power image shows a lumen that is lined by flattened endothelium and contains proteinaceous fluid. Note the lymphocytic aggregate with a germinal center in the connective tissue. Smooth muscle may also sometimes be seen.

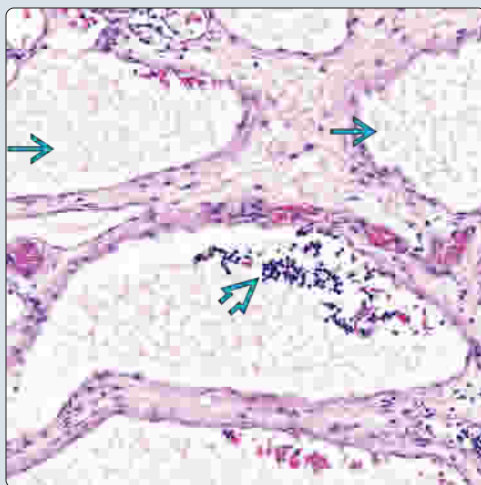


Germinal Center

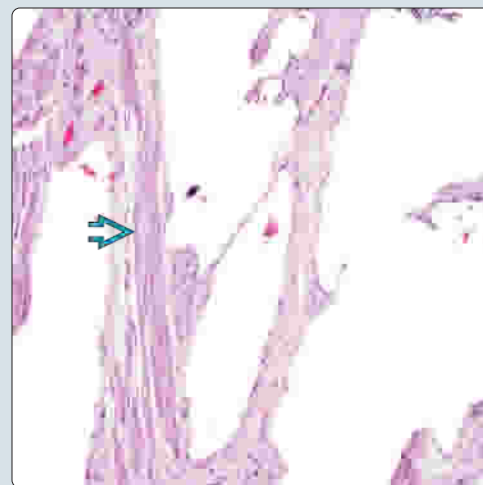


Dilated Lymph-Filled Vessels

(Left) A hematoxylin and eosin image of a lymphangioma shows numerous dilated lymph vessels of varying sizes. The channels are lined by thin endothelium and contain proteinaceous fluid and lymphocytes. (Right) This image shows large endothelially lined spaces with smooth muscle within the wall. It is not unusual to find lumens with numerous red blood cells, which is why a hemangioma may be in the differential diagnosis.



Vessels With Smooth Muscle



TERMINOLOGY

Synonyms

- Cystic hygroma

Definitions

- Malformation of lymphatic system, generally considered congenital
 - Cavernous/cystic: Composed of dilated lymph channels
 - Capillary lesion: Composed of small vessels (dermal type)

ETIOLOGY/PATHOGENESIS

Etiology

- Congenital
 - Associated with genetic syndromes, including Turner syndrome, Noonan syndrome, Maffucci syndrome, trisomies 13, 18, 21
 - Environmental factors
 - Maternal viral infection or substance abuse
- Rare adult lesions likely associated with infection or trauma

CLINICAL ISSUES

Epidemiology

- Incidence
 - 6% of benign tumors of childhood
- Age
 - Often present at birth
 - Usually (~ 90%) diagnosed in first 2 years of life
 - Exceedingly rare in adults

Site

- Head and neck are most common locations
 - Most common in posterior triangle > anterior triangle (more symptoms)
 - Occasionally extend into mediastinum or oral cavity

Presentation

- Large, congenital lesions may be diagnosed prenatally or may result in spontaneous abortion
- Slowly enlarging painless mass
- Large lesions may cause respiratory distress, difficulty swallowing

Treatment

- Surgical approaches
 - Complete resection, although difficult due to adjacent vital structures
- Drugs
 - Intralesional injections of sclerosing agents
 - Bleomycin (BLM); OK-432

Prognosis

- Recurrence rate high if incompletely removed
- Airway obstruction may result in death
- Malignant transformation does not occur

IMAGING

Ultrasonographic Findings

- Used prenatally; cystic lesion, showing size and extent

CT Findings

- Multiple homogeneous cavities
- Nonenhancing, unless there is bleeding into lesion

MACROSCOPIC

General Features

- Variably sized cavities with clear to white fluid

Size

- Often quite sizeable, causing compression of adjacent structures

MICROSCOPIC

Histologic Features

- Variably sized lymphatic spaces lined by endothelial cells
- Lumina contain
 - Lymph, lymphocytes, and erythrocytes
- Large vessels may have smooth muscle layers
- Longstanding lesions may show fibrosis and inflammation

ANCILLARY TESTS

Immunohistochemistry

- **Positive**
 - FVIIIIRAg, CD31, CD34, D2-40 (podoplanin)

DIFFERENTIAL DIAGNOSIS

Hemangioma

- May be difficult distinction, although lacking lymph
- Clinical correlation is helpful

Metastatic Tumor

- Metastatic papillary thyroid carcinoma may often show large cystic space within replaced lymph node
- Lining cells may be attenuated, but TTF-1 &/or thyroglobulin positivity confirms diagnosis

Lymphangiectasia

- May be due to local factors, such as obstruction (e.g., due to tumor), scarring, or previous radiation therapy
- Identical histologic findings; can only be distinguished by clinical history or other findings (if present)

Kaposi Sarcoma

- Generally in different age group and demographic setting
- At least focal areas of typical Kaposi sarcoma seen; infiltrative slit-like spaces lined by hyperchromatic spindle-shaped cells; globules
- **Positive:** HHV8

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5. Okazaki T et al: Treatment of lymphangioma in children: our experience of 128 cases. *J Pediatr Surg.* 42(2):386-9, 2007

KEY FACTS

TERMINOLOGY

- Metastatic carcinoma to neck from unknown primary site (MCUP): Histologic diagnosis of metastatic carcinoma without diagnosis of primary tumor

ETIOLOGY/PATHOGENESIS

- Viral associated (HPV, EBV)
- Tobacco and alcohol abuse


CLINICAL ISSUES

- Painless mass in upper neck
- Jugulodigastric lymph node chain
- 30% of patients never have primary identified
- Radiation is mainstay of therapy
- MCUP: 5-year survival rates range from 18-48%
- HPV-associated squamous cell carcinoma (SCC): Better outcome than non-HPV-associated SCC
- EBV-associated SCC: 65% 5-year survival

MICROSCOPIC

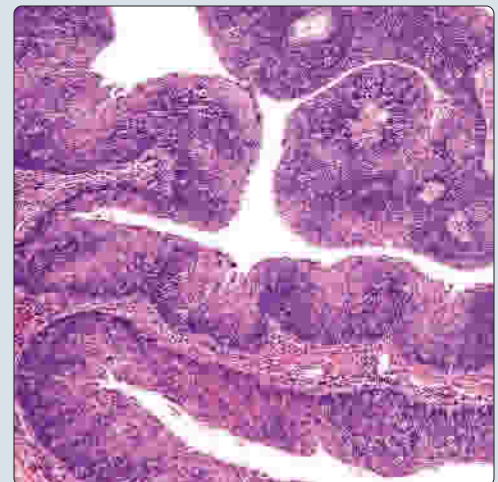
- **Metastatic keratinizing SCC**
 - Presence of keratinization in majority of carcinoma
- **Metastatic nonkeratinizing SCC**
 - Often appears as cystic metastasis with central necrotic material
 - Recapitulates histomorphology of primary oropharyngeal carcinoma
 - Primary tumor may be small and localized deep in tonsillar crypts making clinical detection difficult
- **Metastatic undifferentiated SCC**
 - May appear as cystic metastasis with central necrotic material
 - Histomorphology similar to that of nasopharyngeal carcinoma, undifferentiated type

Cystic Lymph Node




(Left) There is a very thick fibrous connective tissue capsule in this lymph node . There is a large, debris-filled cystic space lined by a ribbon-like epithelium. This is a characteristic appearance for this type of metastatic tumor. **(Right)** There is a ribbon-like or band-like uniformly thick epithelium lining the cystic space. From low power, pleomorphism is difficult to detect.

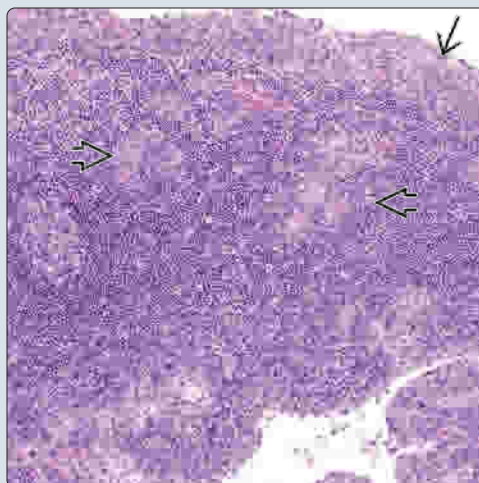


Ribbon-Like or Band-Like Architecture

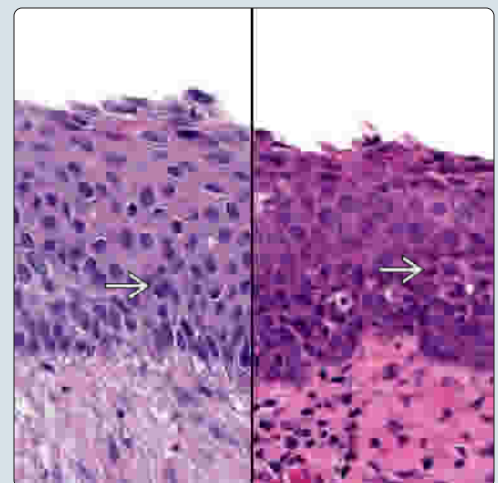


Expansion Into Lymph Node Tissue

(Left) While the epithelium lines a central cyst , it is not uncommon to have the metastatic population  identified deep within the lymphoid stroma, showing an intimate relationship with the epithelium and lymphoid elements. **(Right)** A split field demonstrates very subtle cellular features of a metastatic cystic squamous cell carcinoma (SCC). There is slight pleomorphism, increased cellularity, and isolated mitotic figures  that help to confirm the diagnosis.



Subtle Atypical Features



TERMINOLOGY

Abbreviations

- Squamous cell carcinoma (SCC)

Synonyms

- Metastatic carcinoma to neck from unknown primary site (MCUP)
- Carcinoma of unknown primary (CUP)

Definitions

- Predominantly cystic SCC metastatic to neck lymph nodes
 - Histomorphology of metastases may be divided into
 - Keratinizing SCC
 - Nonkeratinizing carcinoma
 - Undifferentiated carcinoma
- MCUP
 - Histologic diagnosis of metastatic carcinoma without diagnosis of primary tumor

ETIOLOGY/PATHOGENESIS

Etiology

- Tobacco and alcohol abuse
 - Often linked to primary SCC, keratinizing type
 - Primary carcinoma may originate in various mucosal sites of upper aerodigestive tract
 - Histomorphology not specifically linked to any primary site
- Viral related
 - **Human papillomavirus (HPV)**
 - Referred to as HPV-associated SCC, usually nonkeratinizing type
 - p16(+) by immunohistochemistry
 - p16(+) SCC represents reliable predictor of origin from oropharynx (tonsil, base of tongue)
 - Patients typically are nonsmokers and do not abuse alcohol
 - HPV serotype 16 detected by in situ hybridization (ISH) or PCR
 - mRNA E6/E7 HPV ISH is concordant with p16 IHC
 - **Epstein-Barr virus (EBV)**
 - May be referred to as EBV-associated SCC
 - Linked to primary SCC, nonkeratinizing and undifferentiated types
 - Primary cancer may be localized to nasopharynx or other Waldeyer ring sites (tonsil, base of tongue)
 - Positive ISH for Epstein-Barr encoded RNA (EBER)

Origin

- Dedicated lymphatic drainage of neck lymph nodes often (but not always) allows for determination of primary carcinoma site
- Aside from oropharynx and nasopharynx, metastatic SCC to neck lymph nodes may originate from any mucosal site in head and neck
 - Oral cavity, larynx, sinonasal tract most often
- Metastatic thyroid papillary carcinoma may be incidentally identified in neck dissections performed for metastatic SCC
 - Primary thyroid-based papillary carcinoma, usually in ipsilateral lobe

- May be microscopic carcinoma (defined as < 1 cm) and clinically difficult to detect

CLINICAL ISSUES

Epidemiology

- Incidence
 - MCUP
 - Constitutes ~ 3% of all malignant neoplasms
 - As distinct subgroup, represents 2-9% of all H&N cancers
- Age
 - Most frequently 5th-7th decades, peak in 6th decade
 - HPV-associated: Younger patients than non-HPV-associated SCC
- Sex
 - Male > > female (4:1)

Site

- Jugulodigastric lymph node chain
 - Rich lymphatic plexus of Waldeyer ring results in early metastatic disease from small, clinically inapparent tumors
- Can present anywhere within neck, but jugulodigastric lymph node group is most common
 - Level II most common followed by levels I and III
- Isolated nodal mass in submental triangle is rarely carcinoma
 - Typically are inflammatory or related to benign conditions of salivary glands
- Posterior palpable nodes in young patient are usually benign (e.g., inflammatory)

Presentation

- Painless neck mass that has enlarged over recent months
 - Often fixed
 - Usually < 6 months duration
- May have bilateral enlargement in 10% of patients
- When metastasis is diagnosed, primary can be sought
 - Panendoscopy (nasal cavity, nasopharynx, oral cavity, oropharynx, esophagus, larynx)
 - High-resolution PET/CT scans to determine biopsy sites
 - Blind biopsies of various mucosal sites but oropharynx and nasopharynx, specifically
 - Tonsillectomy if biopsies are negative
 - Primaries include base of tongue, lingual or faucial tonsils (Waldeyer ring), nasopharynx, esophagus, and larynx
- Up to 30% of patients never have primary identified
- ~ 30% of patients with metastatic SCC show exclusively **cystic** metastases
- Primaries within tonsil or base of tongue may be very small (< 0.1 cm), making diagnosis difficult

Treatment

- Options, risks, complications
 - Misdiagnosed as primary branchial cleft carcinoma; means that primary is never discovered and continues to grow and metastasize
 - Must do extensive work-up to find primary
 - Panendoscopy, high-resolution PET/CT, and multiple biopsies, including tonsillectomy if needed
- Surgical approaches

- Excision of lymph nodes
- Multiple "blind" biopsies of mucosal sites of upper aerodigestive tract
 - Performed in attempt to find primary carcinoma
- Tonsillectomy performed in biopsies negative for carcinoma
 - Ipsilateral tonsillectomy in presence of unilateral neck disease
 - Bilateral tonsillectomy in presence of bilateral neck disease
- Radiation
 - Mainstay of therapy
 - When primary is identified, IMRT can be used
 - Delivers treatment dose to areas at risk while limiting dose given to normal structures
 - Main advantage is that it spares normal structures (e.g., larynx, parotid), while delivering sufficient radiation dose to areas of gross or clinical disease
 - Brachytherapy
 - Form of radiotherapy where radiation source is placed inside or next to area requiring treatment
 - Can be used alone or in combination with other therapies, such as surgery, external beam radiotherapy, and chemotherapy

Prognosis

- MCUP
 - 5-year survival rates range from 18-48%
 - Dependent on patient and tumor characteristics
- Prognostic factors include
 - Clinical stage of neck
 - Most reliable clinical prognostic indicator
 - Higher clinical stage associated with worse prognosis (decreased survival)
 - Presence of extracapsular spread (ECS)
 - Single most important histologic prognostic factor in recurrent disease, distant metastases, and overall survival
 - Histologic type of metastatic carcinoma
 - HPV-associated and EBV-associated SCC associated with better overall survival than nonviral associated SCC
 - Metastatic adenocarcinoma associated with worse prognosis than metastatic SCC
 - Location of largest lymph node
 - Metastatic carcinoma to supraclavicular or in low cervical lymph nodes rarely cured by any treatment modality
- HPV-associated SCC
 - Radioresponsive cancers
 - Associated with better outcome (better overall and disease-specific survival) than non-HPV-associated SCC possible due to
 - Absence of field cancerization and enhanced radiation sensitivity
 - Highly curable even in presence of advanced disease
- EBV-associated SCC
 - Radioresponsive cancers; ~ 65% 5-year survival

IMAGING

General Features

- High-resolution PET/CT to document cystic mass
- Used to identify possible primary location

MACROSCOPIC

General Features

- Unilocular cyst with thick capsule
- Cyst is filled with grumous, thick, tenacious, purulent yellow to hemorrhagic material
 - May simulate pus or infection

Size

- Mean: 4 cm; range: 1.5-12 cm

MICROSCOPIC

Histologic Features

- **Nodal metastasis**
 - Predominantly cystic
 - Viable cancer may include
 - Keratinizing SCC
 - Nonkeratinizing SCC
 - Undifferentiated SCC
 - Thick, dense, fibrous connective tissue capsule
 - Presence of subcapsular sinus defines structure as lymph node
 - Lymphoid tissue immediately below capsule
 - Often zone of separation between lymphoid stroma and tumor
- **Metastatic keratinizing SCC**
 - Histologic grades include well, moderately, and poorly differentiated
 - Presence of keratinization in majority of carcinoma
 - In poorly differentiated SCC, evidence of keratinization may be minimal
 - Typically associated with desmoplastic tissue response
 - Pattern of carcinoma and presence of desmoplasia contrast to features seen in nonkeratinizing and undifferentiated SCC
- **Metastatic nonkeratinizing carcinoma**
 - Often appears as cystic metastasis with central necrotic material
 - Recapitulates histomorphology of primary oropharyngeal carcinoma
 - Ribbon-like or band-like, uniformly thick epithelium lining cystic spaces, frequently thrown into papillary folds or projections
 - Endophytic pattern can be seen with budding into lymphoid stroma
 - Lacks maturation toward cyst lumen
 - Shows loss of polarity, disorganization and enlarged cells with high nuclear:cytoplasmic ratio
 - May have significant pleomorphism focally or diffusely
 - Limited keratinization
 - Presence of keratinization does **not** exclude diagnosis of nonkeratinizing SCC
 - Transitional-like epithelium with limited atypia may be present
 - Remarkably bland epithelium

- Such benign-appearing epithelium suggests branchial cleft cyst
- Primary tumor may be small and localized deep in tonsillar crypts making clinical detection difficult
- **Metastatic undifferentiated carcinoma**
 - Histomorphology similar to nasopharyngeal carcinoma, undifferentiated type
 - May appear as cystic metastasis with central necrotic material
 - Syncytial growth in form of cohesive nests
 - Neoplastic cells characterized by enlarged nuclei with vesicular chromatin and prominent nucleoli
 - Limited keratinization
 - Presence of keratinization does not exclude diagnosis of undifferentiated SCC
 - Desmoplastic response may be absent
 - Neoplastic cells may be overrun and obscured by benign lymphocytes
- **Posttreatment (irradiation, chemotherapy) metastatic SCC**
 - Early alterations
 - Increase in abnormal nuclear types (macronucleoli, double or multiple nuclei), increased apoptosis, hyperkeratinization
 - Late alterations
 - Necrosis and calcifications, keratin granuloma formation
 - Viable tumor cells may be completely absent or be focally present in association with small islands of residual intact tumor
 - In absence of malignant cells, keratin granuloma may be replaced by fibrotic acellular nodules

ANCILLARY TESTS

Cytology

- Smears quite cellular, dominated by anucleate squamous and debris
- Rare fragments of atypical squamous epithelium
- Isolated, individual atypical keratinocytes with nuclear atypia, increased nuclear:cytoplasm ratio, hard keratinization, and irregular cell shape (tadpole cells)
- Must have more than just isolated atypical cells to confirm diagnosis

Immunohistochemistry

- **Positive:** CK-PAN, CK5/6, CK8, CK14, CK19, p63, p40
- **Negative:** CK7, CK20, EMA
- **HPV-associated SCC**
 - **Positive:** p16 in > 70% of cells with nuclear and cytoplasmic staining (surrogate marker for HPV-associated carcinomas)
 - Reliable predictor of origin from oropharynx
- **EBV-associated SCC**
 - **Positive:** EBER (IHC or ISH) nuclear reaction
- **Lymphoepithelial carcinoma** (nonkeratinizing) may be EBER or p16(+), depending on site of origin
 - Do sequential or concurrent staining as suggested by clinical or imaging findings
- **Posttreatment metastatic SCC**
 - CK-PAN, CAM5.2, CK5/6, p63, and p40 may aid in identifying viable malignant cells or keratin granuloma

DIFFERENTIAL DIAGNOSIS

Branchial Cleft Cyst

- Benign epithelium lining cystic spaces, usually showing intimate admixture of epithelium with stroma
- Maturation is noted without atypia or mitotic figures
- Lacks desmoplastic or thickened fibrous capsule
- May show interdigitating p16(+) cells

Primary Branchiogenic Carcinoma

- Does not exist

Thymopharyngeal Cyst

- Thymic gland tissue within lesion confirms this cyst type

Malignant Proliferating Pilar Tumor

- More common in women, > 90% on scalp, with multicystic, dermal-based tumor
- SCC appearance, **positive:** p16, CK5/6, p63, but lacking nodal architecture

Metastatic Cystic Papillary Thyroid Carcinoma

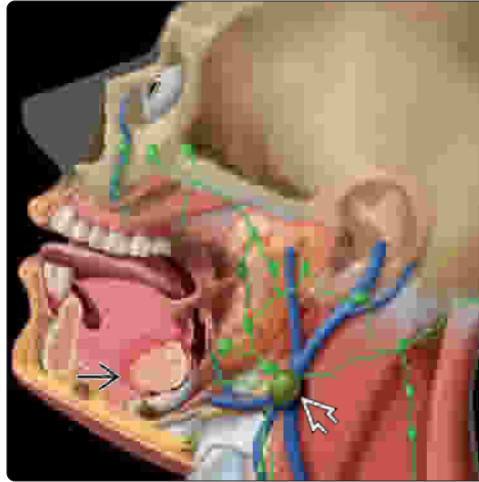
- Lateral neck, frequently large cyst; flattened cuboidal epithelium, with nuclear features of metastatic cystic papillary thyroid carcinoma
- **Positive:** TTF-1, thyroglobulin, pax-2; **negative:** p16

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Base of Tongue Lymphatic Drainage

(Left) There is a small but well-defined carcinoma at the base of the tongue that has developed a lymph node metastasis to the jugulodigastric lymph node. This level II lymph node is a characteristic metastatic location. (Right) The FDG PET technique (left) shows a very high standardized uptake value (SUV) in the cervical lymph nodes, reflecting metastatic disease. The PET/CT fusion study (right) highlights the area of metastatic tumor with the lymph nodes affected.

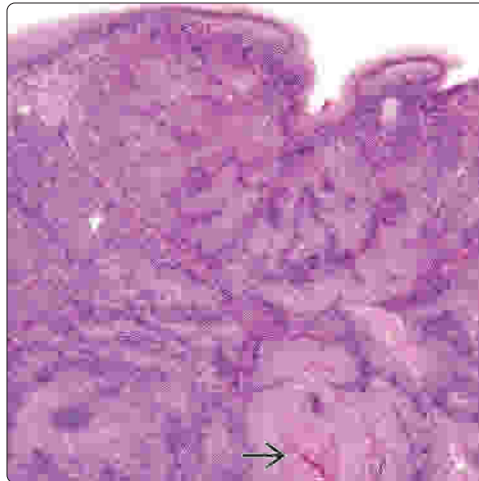


Metastatic Cystic Squamous Cell Carcinoma

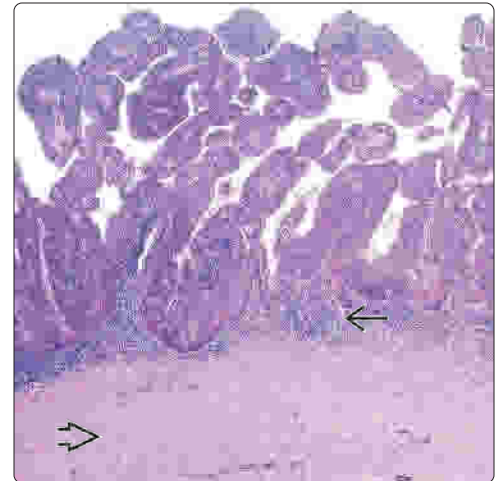


Inverted Pattern of Growth

(Left) In this example, there is a lining epithelium that plunges down into the lymphoid stroma of the lymph node, creating islands and nests of tumor. However, they still show a ribbon-like appearance, focally showing necrosis. (Right) The lymph node capsule is greatly thickened with only a limited amount of lymphoid tissue remaining. In this example of metastatic cystic SCC, the papillary projections are quite complex.

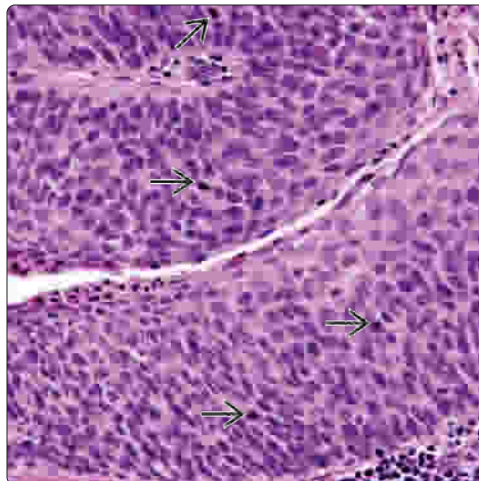


Papillary Projections Into Cyst Lumen

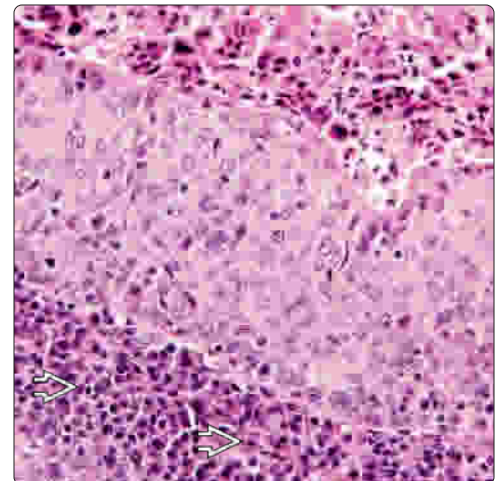


Increased Mitoses in Metastatic Squamous Cell Carcinoma

(Left) The epithelium shows a subtle increased cellularity, lacking significant maturation toward the surface and including a number of mitoses. This would not be seen in a branchial cleft cyst. (Right) In some cases, the epithelium is associated with significant keratin debris, which is sloughed into the lumen of the cystic metastasis. The epithelium is atypical in this high-power field. Lymphoid elements are noted at the basal zone.



Dyskeratosis and Keratin Debris



Focal Keratinization

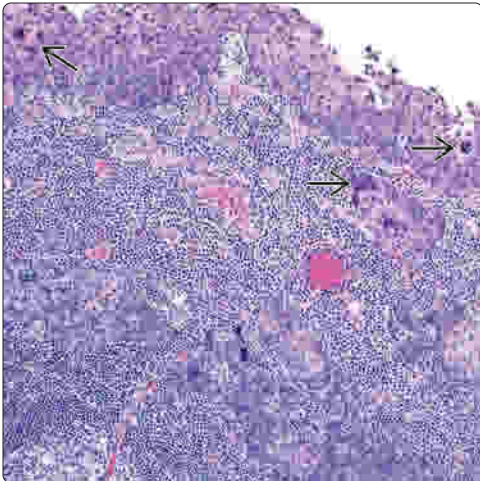


Metastatic Keratinizing Squamous Cell Carcinoma

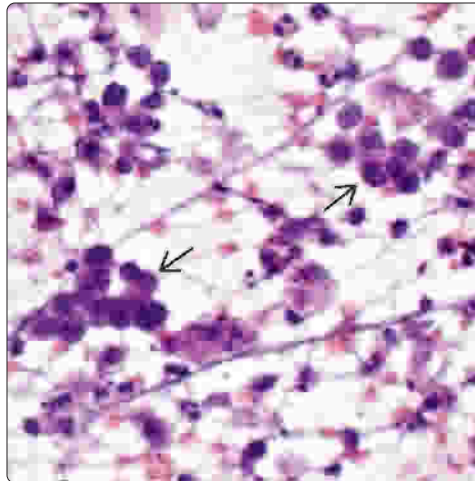


(Left) The ribbon-like growth is noted in this field, associated with focal areas of keratinization or dyskeratosis. The epithelium is thickened with focal atypia. **(Right)** Metastatic cystic keratinizing SCC to a cervical lymph node is confined to the lymph node without extranodal capsular extension.

Highly Atypical Squamous Epithelium

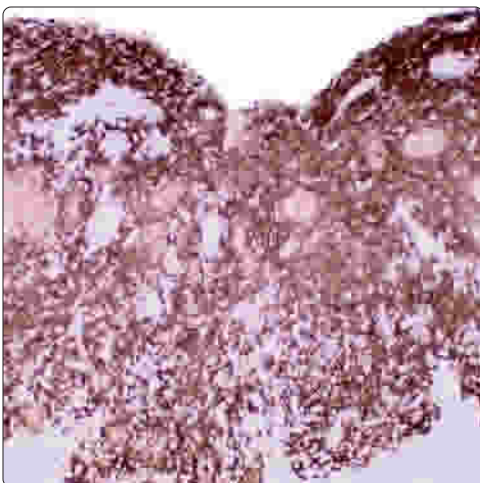


Loosely Cohesive Atypical Epithelium

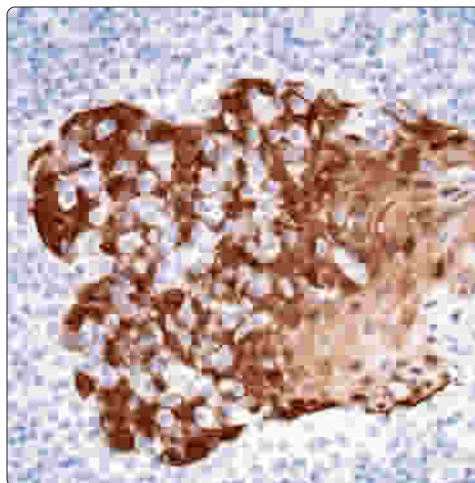


(Left) In some cases, there is easily identified pleomorphism within the neoplastic population, as noted in this example. Profound pleomorphism helps to confirm the diagnosis. **(Right)** There is a background of degenerated debris in this cytology preparation, but the loosely cohesive atypical epithelial groups are easily identified in this example of metastatic cystic SCC.

Strong, Diffuse p16 Immunoreactivity



Interdigitating Lymphocytes



(Left) This metastatic SCC shows a strong and diffuse nuclear and cytoplasmic immunoreactivity with p16, helping to suggest an oropharyngeal primary site. p16 reactions can be seen in other tumor types, but in the correct clinical setting are diagnostic of an HPV-related tumor. **(Right)** There is a strong and diffuse nuclear and cytoplasmic reaction with p16 in this metastatic focus of SCC, but the intimate relationship with the lymphocytes can be seen as the negative reaction in the lymphocyte nuclei.

KEY FACTS

TERMINOLOGY

- Mesenchymal spindle cell neoplasm with variable epithelial differentiation and specific chromosomal translocation: $t(X;18)(p11.2;q11.2)$

CLINICAL ISSUES

- No association with synovium or bursa
- Bimodal presentation
 - 15-35 and ~ 50 years
- ~ 10% develop in head and neck
- Male > Female = 3:1
- Head and neck mucosal tumors tend to have better prognosis than soft tissue counterparts

IMAGING

- Soft tissue mass, frequently with calcifications

MACROSCOPIC

- Range: 1-12 cm; mean: ~ 5 cm

MICROSCOPIC

- Separated into monophasic and biphasic
 - Epithelial &/or spindle cell components
 - Creates glandular appearance with lumina
- Marbled spindled areas
 - Alternating light and dark areas
 - Spindled cells are uniform with indistinct cell boundaries
- Hemangiopericytoma-like vasculature may be seen
- Mitotic figures are identified but not usually increased

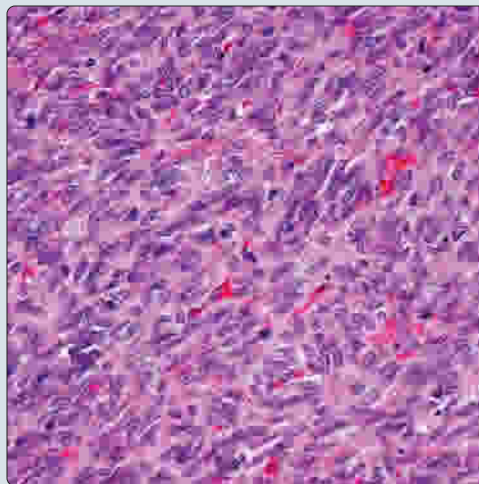
ANCILLARY TESTS

- Positive: TLE1, EMA, pancytokeratin
- Classically show $t(X;18)(p11.2;q11.2)$

TOP DIFFERENTIAL DIAGNOSES

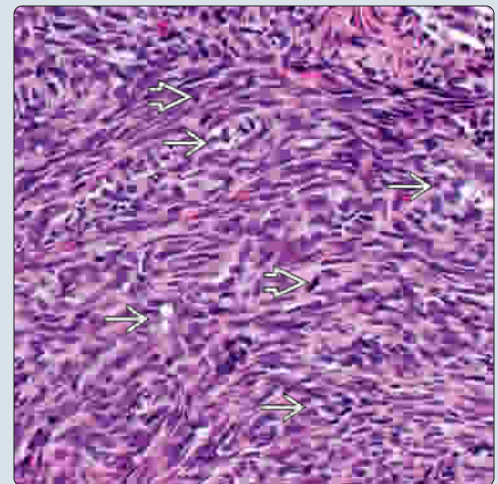
- Spindle cell (sarcomatoid) squamous cell carcinoma, malignant peripheral nerve sheath tumor, fibrosarcoma, mucosal melanoma, leiomyosarcoma, epithelioid sarcoma

Monophasic Spindle Cell Synovial Sarcoma

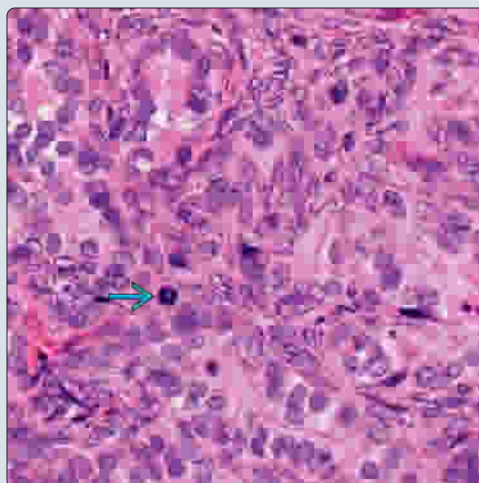


(Left) This monophasic synovial sarcoma (SS) shows a densely packed, interlacing spindle cell proliferation with monotonous cells arranged in a syncytium. The nuclei are ovoid, pale staining with small nucleoli. There is a rich vascularity. (Right) A biphasic SS shows an admixture of epithelial and spindle cell components. The epithelial cells have abundant cytoplasm, creating a glandular appearance with lumina. Mitotic figures are identified.

Biphasic Synovial Sarcoma

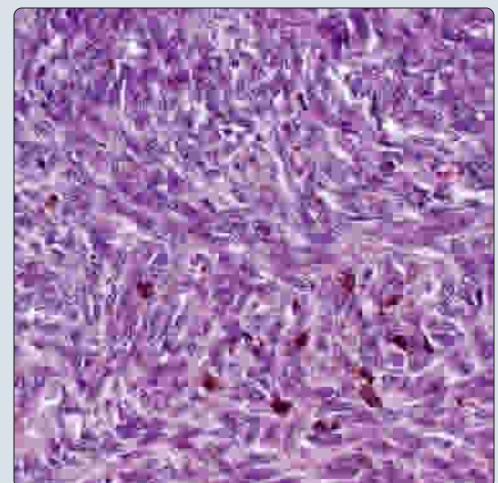


Mitotic Figure in Biphasic Synovial Sarcoma



(Left) There is a predominantly glandular appearance to the proliferation in this high-power field of a biphasic SS. There is a pale appearance to the nuclei. Note the mitotic figure. (Right) There is a short, interlacing fascicular appearance to this SS. There are several areas that contain melanin pigment, an unusual finding in this tumor.

Pigmentation in Some Synovial Sarcoma



TERMINOLOGY

Abbreviations

- Synovial sarcoma (SS)

Synonyms

- Tendosynovial sarcoma, synovial cell sarcoma, malignant synovioma, synovioblastic sarcoma

Definitions

- Mesenchymal spindled cell neoplasm with variable epithelial differentiation and specific chromosomal translocation: t(X;18)(p11.2;q11.2)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Up to 10% of soft tissue sarcomas
 - ~ 10% develop in head and neck
- Age
 - Bimodal presentation
 - Young adults (15-35 years; mean: 25 years)
 - Older age (around 50 years)
- Sex
 - Male > female = 3:1

Site

- No association with synovium or bursa
- Parapharyngeal space, oropharynx, and hypopharynx/larynx
- Direct extension into larynx may be initial presentation

Presentation

- Nonspecific, usually related to anatomic site
- Mass, hoarseness, and dysphasia
- Pain may be present
- Most patients present at high stage

Treatment

- Surgical approaches
 - Need aggressive wide surgical resection with meticulous attention to surgical margins
- Adjuvant therapy
 - Combined with radiation
- Radiation
 - Combined with chemotherapy

Prognosis

- Head and neck mucosal tumors tend to have better prognosis than soft tissue counterparts (60% 5-year survival)
- Recurrences in ~ 25% of patients (especially if positive margins)
- Metastatic disease in ~ 25% of patients (lung)
- ~ 1/3 of patients die from disease
- Best outcome: Small tumors, pediatric patients, calcifications, mitotically inactive tumors, completely resected (negative margins)
- Patients with SSX2 gene tend to have better prognosis

IMAGING

General Features

- Soft tissue mass, frequently with calcifications
- Frequently multilobulated with heterogeneity
 - Hemorrhage, fluid levels, and septa
- May have well-defined margins

CT Findings

- Gives information about site of origin and size/extent
- Spiculated, irregular calcifications in ~ 20% of cases

MACROSCOPIC

General Features

- Pedunculated or polypoid within mucosal sites
- Mass is usually circumscribed but can be infiltrative
- Multinodular and may be multicystic
- Cut surface yellow, gray, gritty to boggy
- May have mucoid or hemorrhagic degeneration

Size

- Range: 1-12 cm; mean: ~ 5 cm

MICROSCOPIC

Histologic Features

- Separated into monophasic and biphasic
 - In head and neck, monophasic spindled is most common type
- Biphasic
 - Has epithelial and spindled cell components
 - Variable proportions of each component
 - Epithelial cells have abundant cytoplasm
 - Creates glandular appearance with lumina
 - May have papillary projections or pseudoglandular spaces
 - Epithelial component may predominate
- Densely packed, short fascicles
 - May be marbled: Alternating light and dark areas
- Hemangiopericytoma-like vasculature may be seen
 - Rich vascularity is noted
- Spindled cells are uniform with indistinct cell boundaries
- Nuclei are ovoid, pale staining with small nucleoli
- Mitotic figures are identified but not usually increased
- Stromal collagen is wiry and scant
- Myxoid change may be seen
- Calcifications are noted
- Mast cells are usually easy to identify

ANCILLARY TESTS

Cytology

- Yield is usually high, with cellular smears
- 3D, densely cellular tumor tissue fragments with irregular borders in almost all cases
 - Vascular plexus or network within tissue fragments
 - Pericapillary arrangement is common
- Dispersed cells in background, often with naked (striped) nuclei
- Tumor cells are small to medium, monomorphic, and bland

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
TLE1	Positive	Nuclear	Nearly all tumor cells
CK-PAN	Positive	Cytoplasmic	Epithelial cells; isolated spindle cells
CK7	Positive	Cytoplasmic	Epithelial and spindle cells
CK19	Positive	Cytoplasmic	Epithelial and spindle cells
EMA	Positive	Cytoplasmic	Glandular lumina and slit-like spaces
S100	Positive	Nuclear & cytoplasmic	~ 30% of cases
CD99	Positive	Cytoplasmic	~ 60% of cases
Bcl-2	Positive	Cytoplasmic	Especially spindle cells
Vimentin	Positive	Cytoplasmic	Especially spindle cells
CD34	Negative		
Desmin	Negative		

- Cells are spindled to club-shaped, arranged in fascicles or whorls
 - Nuclei are fusiform, ovoid to rounded
 - Nuclear chromatin is bland
 - Nucleoli may occasionally be present
- Small gland-like structures can be seen (only in epithelioid-biphasic type)
 - Polygonal cells separated from spindle cells
- Amorphous, hyaline matrix material may be mixed with cells
 - Collagenous stroma, hyalinized to fibrillar
 - May yield rosette-like structure with cells surrounding central pink material
- Mast cells may be present
- Poorly differentiated and myxoid variants may be difficult to diagnose on cytology
- FISH for translocation can be performed on FNA material

Immunohistochemistry

- Epithelial markers within spindled and epithelial components

Genetic Testing

- Classic t(X;18)(p11.2;q11.2)
 - FISH break-apart probe is best
- SSX1*, *SSX2*, *SSX4* from X chromosome
 - Vast majority accounted for by *SSX1*
- SS18* from chromosome 18

DIFFERENTIAL DIAGNOSIS

Spindle Cell (Sarcomatoid) Squamous Cell Carcinoma

- Tends to be mucosal primary
- Positive:** Keratin, EMA, CK1, CK5/6, p63, p40

Fibrosarcoma

- Herringbone, long fascicles; **positive:** Vimentin only

Malignant Peripheral Nerve Sheath Tumor

- Can be almost indistinguishable, as both have marbling pattern
- Positive:** S100 protein, SOX10

Leiomyosarcoma

- More whorled appearance with blunted nuclei with perinuclear cytoplasmic clearing
- Positive:** Desmin, SMA, MSA

Mucosal Malignant Melanoma

- Can be histologic mimic
- Positive:** S100 protein, SOX10, melan-A, HMB45

Hemangiopericytoma ↔ Solitary Fibrous Tumor

- Hemangiopericytoma will have patternless appearance, with collagen deposition
- Vascularity may be similar
- Positive:** STAT6, CD34, Bcl-2, CD99

Epithelioid Sarcoma

- Usually does not develop in head and neck locations
- Will have biphasic appearance with similar immunohistochemistry
- Lacks characteristic translocation of SS

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MR T1WI of Soft Tissue Synovial Sarcoma



Nodular and Circumscribed Gross Tumor

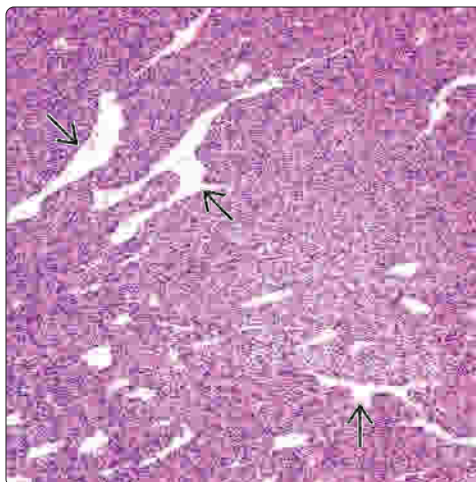


(Left) Typical MR of SS of the masticator space is shown. Axial T1WI MR better shows the soft tissue extent of the masticator space SS. The bony central area is visible as a very low-signal component of the tumor. (Right) The neck mass is circumscribed, showing a slightly nodular appearance, with several cysts. The cut surface shows bright yellow and gray areas. This tumor was ~ 4 cm.

Marbled Appearance

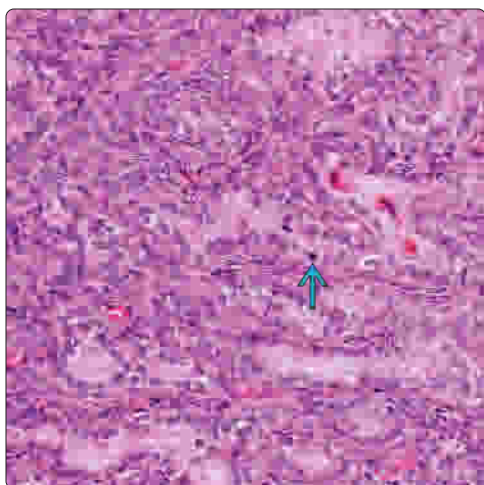


Prominent Vascular Pattern

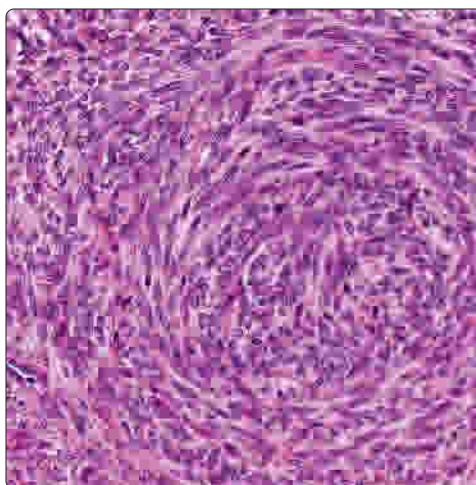


(Left) One of the characteristic features for an SS is a marbled appearance, with alternating light and dark areas created by the short fascicles. The spindled cells are uniform. This pattern may also be seen in malignant peripheral nerve sheath tumors. (Right) This monophasic SS shows the spindled cells arranged around hemangiopericytoma-like vasculature. This pattern is seen in many different tumor types and is not specific. However, SS usually has a rich vascularity, as seen here.



Glandular Pattern



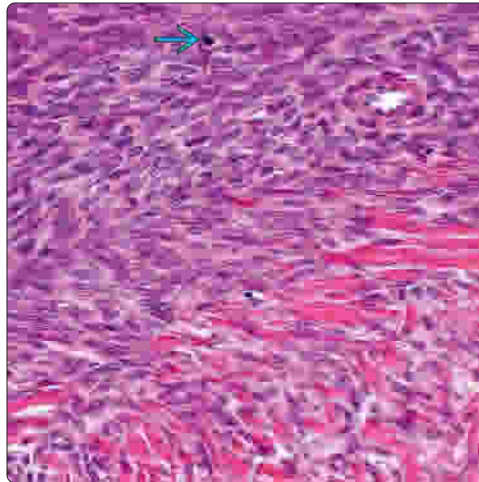
Whorled Appearance of Synovial Sarcoma



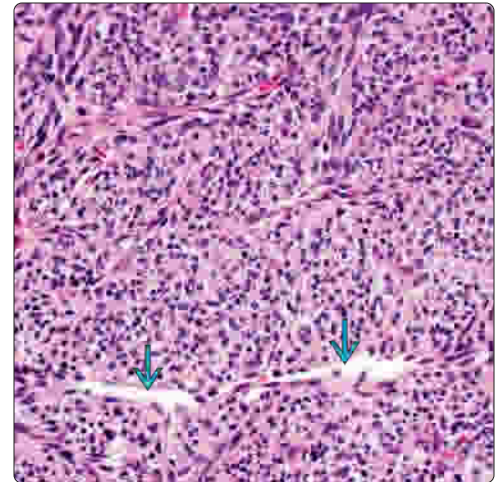
(Left) There is a prominent glandular epithelial appearance to this biphasic SS. The glands are separated by a spindled cell population. Isolated glandular mitoses can be seen. (Right) The spindled cell population can show a variety of different patterns of growth. Here, a whorled appearance predominates. There is also a rich vascular plexus, easily identified throughout this image.

(Left) The densely packed, short, interlacing fascicles of this monophasic SS blend with wiry stromal collagen. Mitoses  are usually easy to find although they are not usually increased. **(Right)** The interlaced fascicles can give an end-on or longitudinal appearance, simulating neural or smooth muscle tumors. There is a patulous vessel  in this tumor, a frequent finding in SS.

Collagen Fibers With Spindled Cells

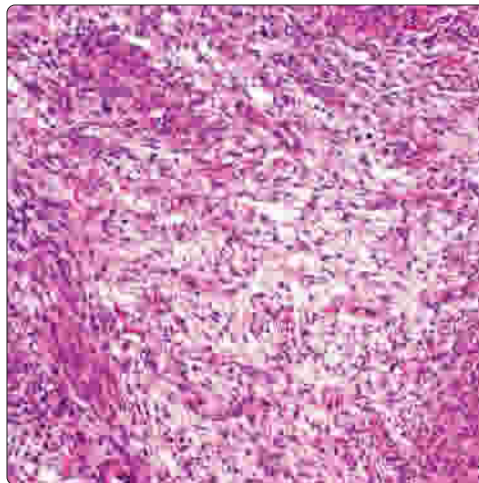


Interlaced Fascicles

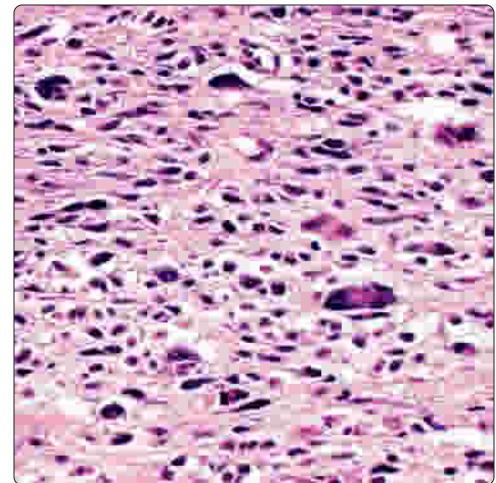




(Left) Monophasic spindled SS may undergo myxoid change and degeneration. True tumor necrosis is rarely seen. This appearance can simulate Antoni B areas of a peripheral nerve sheath tumor. **(Right)** Cellular pleomorphism is uncommon in SS and tends to be a localized phenomenon. This photograph shows a small collection of highly pleomorphic tumor cells. This was an isolated finding within a biphasic SS. Some view this as an "ancient" change phenomenon.

Myxoid Degeneration

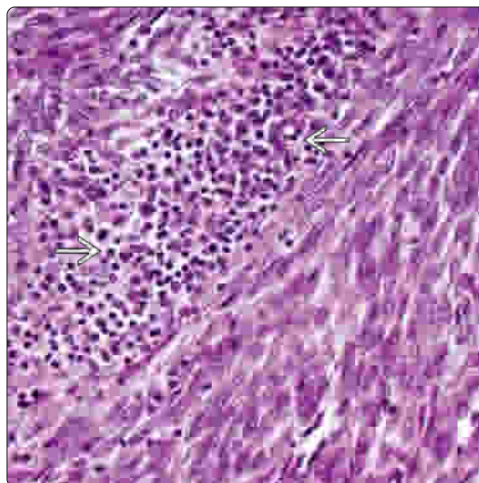


Pleomorphic Ancient Cells

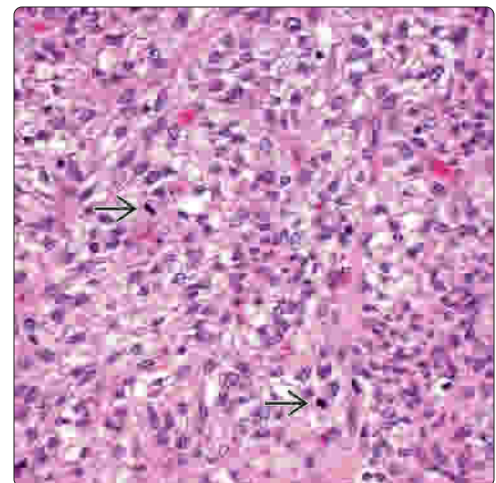


(Left) A monophasic spindled SS shows high cellularity, along with numerous inflammatory cells . Inflammatory cells are uncommon, although mast cells are frequently seen. **(Right)** There is a vague monotony to the cellular population, here shown with cytoplasmic clearing in this SS. Mitoses are also noted  although they are not atypical.

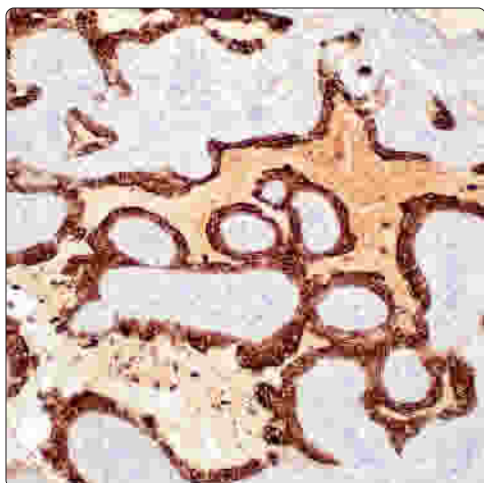
Inflammatory Cells in Synovial Sarcoma



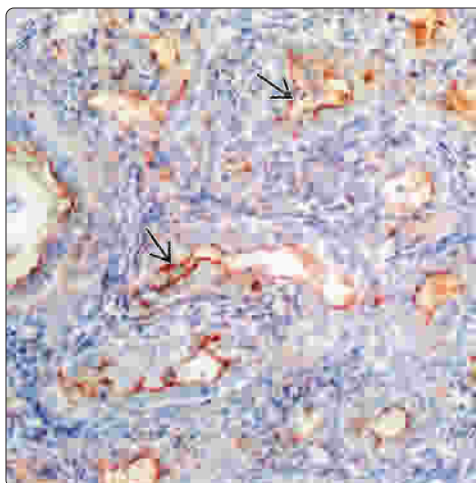
Monotonous Neoplastic Cells



CK-PAN Strongly Highlights Glandular Cells

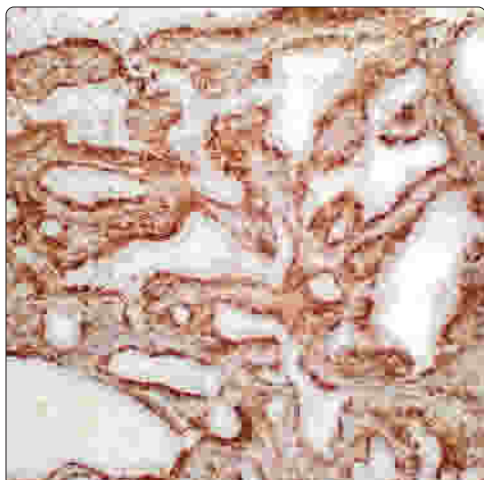


EMA Cytoplasmic Epithelial Reaction

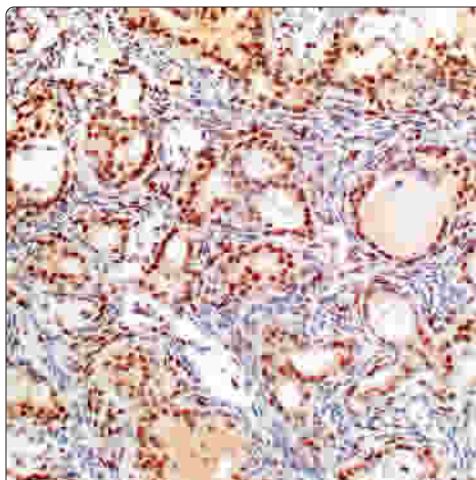


(Left) In this biphasic SS, the keratin decorates the cytoplasm of epithelial cells without staining the spindle cells. Each of the keratin immunohistochemical antibodies (CK7, CK19, EMA) has a slightly different reaction pattern. **(Right)** This biphasic SS demonstrates a positive cytoplasmic reaction in the glandular lumina with EMA. This type of luminal reaction is characteristic for this marker.

Bcl-2 Spindle Cell Reaction

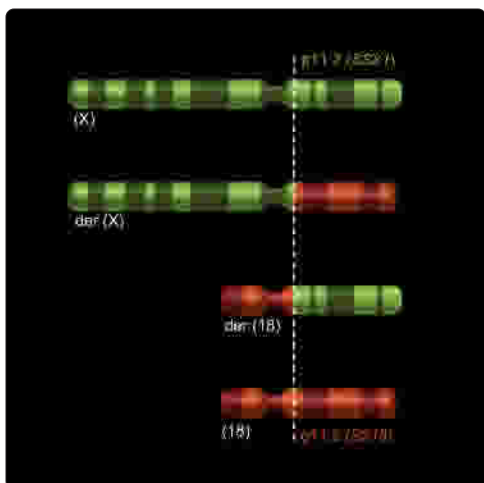


TLE1 Nuclear Reaction

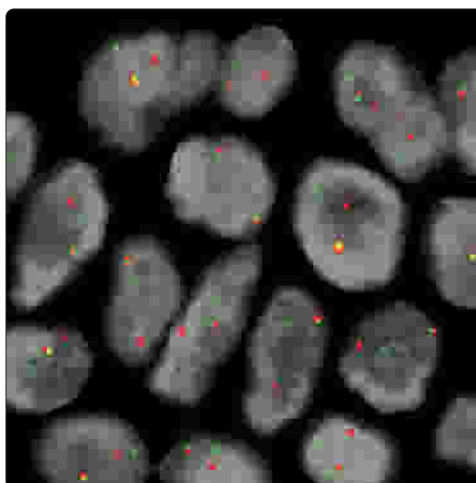


(Left) Bcl-2 is not a specific or sensitive marker for SS but shows a strong and diffuse cytoplasmic reaction within the spindle cells specifically. Vimentin shows a similar reaction profile. **(Right)** The neoplastic cells show a strong and diffuse nuclear reaction with transcription factor TLE1. This is a very helpful marker to confirm the diagnosis by immunohistochemistry.

t(X;18) Translocation Graphic



FISH Break-Apart Probe for Synovial Sarcoma



(Left) The characteristic translocation $t(X;18)(p11.2;q11.2)$ of the SSX1 gene (chromosome X, green) and SS18 gene (chromosome 18, red) is present in > 95% of SSs (translocation shown in the center). The fusion protein can be detected by a FISH probe. **(Right)** A FISH break-apart probe can be performed on paraffin-embedded material to highlight the translocation between SSX1 and SS18. Single red and green signals in each cell confirm the break apart (yellow signal is normal).

KEY FACTS

TERMINOLOGY

- Low- to intermediate-grade malignant tumor that recapitulates embryonic notochord
- 3 groups: Sacrococcygeal, craniocervical, vertebral

CLINICAL ISSUES

- May occur at any age, but 4th decade peak for head and neck primaries
- Male > female (5:3)
- Surgery is treatment of choice, with postoperative radiation
- Prognosis based on site, completeness of resection, age, gender, and whether radiation is employed
- Recurrences are common (years after treatment)

IMAGING

- Expansile, lytic, destructive soft tissue mass with extensive bony erosion

MACROSCOPIC

- Lobulated tumors, gelatinous, slippery, and mucoid

MICROSCOPIC

- Histologically stratified into classic, chondroid, and dedifferentiated
- Lobular growth, arranged in cords, clusters, islands
- Epithelioid polygonal cells with hyperchromatic nuclei
 - Pleomorphism can be considerable
- Large physaliphorous cells with multivacuolated cytoplasm
- Abundant intercellular mucinous matrix



ANCILLARY TESTS

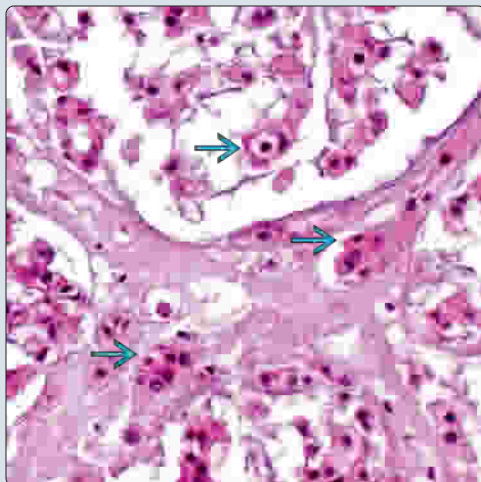
- **Positive:** Brachyury, pan-cytokeratin, epithelial membrane antigen (EMA), S100 protein; **negative:** GFAP

TOP DIFFERENTIAL DIAGNOSES

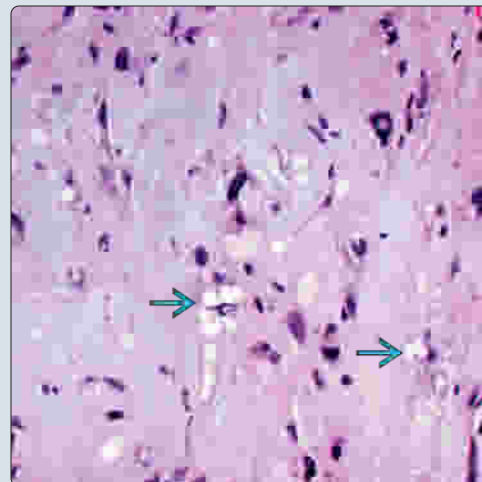
- Chondrosarcoma, mucinous adenocarcinoma, chordoid meningioma, chordoid glioma, liposarcoma, myoepithelioma/myoepithelial carcinoma, extraskeletal myxoid chondrosarcoma

Chief Cells in Lobular Cluster


(Left) Histologically, chordomas are composed of 2 cells types, eosinophilic chief cells  and physaliferous cells set within a myxoid background matrix. The cells are arranged in nests and cords. (Right) There is a rich myxoid background surrounding atypical epithelioid polygonal cells. Intranuclear inclusions are seen. Physaliphorous cells  with vacuolated cytoplasm are noted.

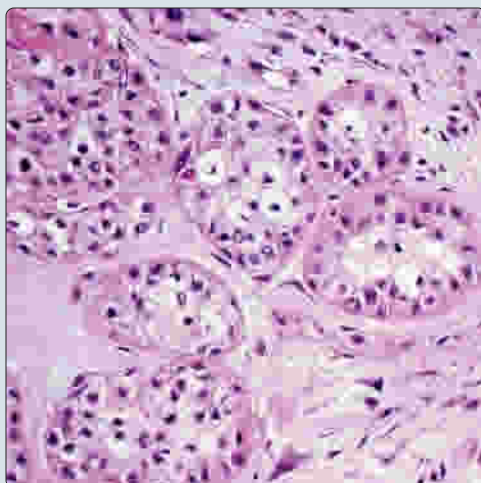


Physaliphorous Cells in Chordoma

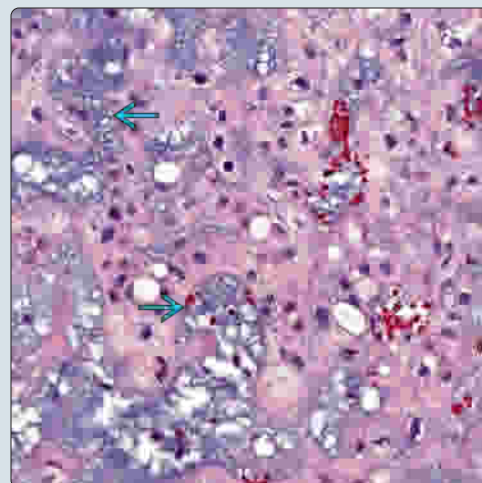


Cluster/Island of Neoplastic Cells

(Left) A lobular, nested appearance of these epithelioid cells showing uniform nuclei with mild pleomorphism. There is ample eosinophilic to cleared cytoplasm in this chordoma. (Right) Cords or hepatoid columns of neoplastic polygonal cells with limited pleomorphism are noted within a myxoid background  in this classical chordoma.



Myxoid Background



TERMINOLOGY**Definitions**

- Low- to intermediate-grade malignant tumor that recapitulates embryonic notochord
 - Divided into 3 broad groups
 - Sacrococcygeal (60%)
 - Craniocervical (sphenoccipital) (25%)
 - Vertebral (15%)

ETIOLOGY/PATHOGENESIS**Developmental Anomaly**

- Neoplastic transformation from vestigial remnants of embryonic notochord tissue
- Notogenesis begins by 3rd gestational week
 - Superior notochord limit: Rathke pouch
 - Lies at level of sphenoid
 - If persistent notochord canal, may result in Tornwaldt cyst
 - Inferior notochord limit: Coccyx
 - Extends entire length of future vertebral column
 - Becomes enveloped by developing vertebral bodies derived from mesoderm
- Notochord involutes during 8th week of development
- Incomplete regression of notochordal tissue can result in chordoma
- Overexpression of transcription factor brachyury (gene product of *T*)

Familial

- Limited number with familial association (autosomal dominant)

CLINICAL ISSUES**Epidemiology**

- Incidence
 - ~ 0.05/100,000 population/year
 - ~ 2% of all malignant bone tumors
 - ~ 0.2% of all nasopharyngeal tumors
- Age
 - May occur at any age, but 4th decade peak for head and neck primaries
 - Clivus-based tumors: Peak 20-40 years
- Sex
 - Male > female (5:3)

Site

- Within craniocervical sites
 - Dorsum sellae, clivus, retropharyngeal
 - Nuclei pulposi of cervical vertebrae
 - Ectopic
 - Frontal sinuses, other paranasal sinuses, mandible

Presentation

- Symptoms are usually nonspecific
 - Headaches, pain (type depends on tumor location)
 - Diplopia (abducens nerve, often left-sided), visual loss, visual field defects
 - Neurologic symptoms from local compression (nerve impingement)

- Cranial nerve deficits (most commonly 3rd and 6th cranial nerves), sensorimotor deficits, hearing loss, tinnitus, ataxia, dizziness, hydrocephalus
- Mass, especially if in parapharyngeal space
- Nasal obstruction, discharge, anosmia, nasal speech, epistaxis
- Dysphagia, dyspnea, dysphonia
- Tumors are slow growing, resulting in local spread
 - Locally destructive
 - Rarely exhibit lymphatic &/or hematogenous dissemination
- Endocrinopathies due to sella turcica invasion

Treatment

- Options, risks, complications
 - Transient complications may include cerebrospinal fluid leak with meningitis, nerve paralysis/paresis: 5th, 6th, and 7th nerves, oronasal fistula, epistaxis
- Surgical approaches
 - Surgery is treatment of choice
 - Because of anatomic location, complete (gross total) resection is difficult
 - Approaches based on anatomic site: Open vs. endoscopic, often staged
- Drugs
 - Chemo-resistant tumors, usually lacking even palliative response
- Radiation
 - Postoperative radiotherapy is usually employed
 - Tends to be radioresistant, requiring high dose for good response
 - Complications include hypopituitarism, memory impairment, oculomotor impairment, severe hearing loss, bilateral visual loss

Prognosis

- Prognosis based on site, completeness of resection, age, gender, and whether radiation is employed
 - Aggressive surgery and radiation: 50-75% 5-year survival; 45-65% 10-year survival
 - Incomplete excision with conventional radiation: 20% 5-year survival
 - Radiation therapy alone: 30% survival
 - Up to 60% of patients ultimately die from disease, due to recurrences
- Recurrences are common and may be observed many years after treatment
 - Patients may survive for years after recurrence
 - Up to 88% recurrence rate at 10 years
- Metastases are uncommon (< 10% of cases)
 - Lung, bone, liver, soft tissue
- Prognostic indicators
 - Tumor location, size, resectability, dedifferentiated type, gender, age
 - Chondroid variant has slightly better prognosis
- When genetic abnormalities are present, there is increased incidence of recurrence, disease progression, and poor survival

IMAGING

General Features

- Best studies: CT & MR are complementary
 - Bone CT for bone changes and MR for soft tissue extent
- Destructive lesion with large, well-defined, T2 hyperintense, enhancing soft tissue mass on MR
- May extend along nerve roots
- May enlarge neural foramina (mimic of peripheral nerve sheath tumors)

Radiographic Findings

- Expansile, lytic, destructive soft tissue mass with extensive bony erosion including into sella turcica
- Osteolysis is well circumscribed, without osteosclerotic rim
 - Sclerosis of vertebral body is usually seen
- Coarse, amorphous tumor calcifications (site specific)
 - Sacrococcygeal (90%)
 - Clival (50-60%)
 - Vertebral (30%)

MR Findings

- Homogeneously isointense with muscle on T1-weighted studies
 - Moderate enhancement after gadolinium injection
- Hyperintense on T2-weighted studies (same intensity as CSF)
 - Similar to nucleus pulposus

CT Findings

- Heterogeneous mass, similar signal to muscle
- Tumor calcifications are highlighted

Bone Scan

- Cold lesion usually

MACROSCOPIC

General Features

- Expansive, lobulated tumors
- Cut surface is gelatinous, slippery, mucoid to myxoid
- Gritty areas due to calcifications

Sections to Be Submitted

- 1 section per cm

Size

- Range: 1.5-15.0 cm
 - Median: 4 cm
- Tumor volume: 2-125 cm³
 - Median: 21 cm³

MICROSCOPIC

Histologic Features

- Histologically stratified into classic, chondroid, and dedifferentiated
- Classical chordoma shows 4 major histologic features
 - Lobular growth
 - Arranged in cords, clusters, islands, "hepatoid" columns
 - Epithelioid polygonal cells, which may be slightly elongated

- Nuclei are intermediate size, hyperchromatic, often with small nucleoli or nuclear pseudoinclusions
- Pleomorphism can be considerable
- Tumor cells may "wrap" around or "hug" one another
- Large physaliphorous cells
 - Characteristic round vacuoles in the cytoplasm, creating bubbly appearance
 - From Greek meaning "bearer of bubbles"
 - Cytoplasm filled with mucin
 - May show large, single vacuole, a mimic of adipocyte
- Abundant intercellular mucinous matrix surrounds epithelioid cells, creating frothy myxoid appearance
- Limited mitoses
- Vascular invasion can be seen

Chondroid Chordoma

- Hyaline-type chondroid or cartilaginous tissue
- Only seen in about 5% of chordomas
- More common in women and younger patients

Dedifferentiated Chordoma

- Conventional chordoma in association with sarcomatous elements
 - Malignant fibrous histiocytoma
 - Fibrosarcoma
 - High-grade chondrosarcoma
 - Osteosarcoma
- Seen in ~ 5% of chordomas
- Necrosis, when present, suggests an aggressive course

ANCILLARY TESTS

Cytology

- Smears are usually moderately to highly cellular
 - Physaliferous cells are usually easily identified
 - Finely bubbled cytoplasm
 - Larger than chief cells
 - Epithelioid chief cells
 - Eosinophilic cytoplasm
 - Regular chromatin distribution
 - Intranuclear cytoplasmic inclusions
- Myxoid or chondromyxoid background matrix
- Mitotic figures are rarely identified

Histochemistry

- Mucin positive with mucicarmine and periodic acid-Schiff

Immunohistochemistry

- **Positive:** Brachyury, pan-cytokeratin, epithelial membrane antigen (EMA), S100 protein; **negative:** GFAP

Genetic Testing

- Suggested **genesis** or **progression** candidates on chromosome 7q33
 - Sonic hedgehog homolog (SHH) protein is key in regulating notochord and vertebral body development gene, found on chromosome 7
- There is wide variety of complex karyotypic abnormalities
- Recurring single nucleotide polymorphism (SNP), rs2305089 that lies in exon 4, encodes part of DNA binding domain of Brachyury
- Absence or loss of fragile histidine triad (FHIT) protein

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
AE1/AE3	Positive	Cytoplasmic	All tumor cells
CK-PAN	Positive	Cytoplasmic	All tumor cells
CK8/18/CAM5.2	Positive	Cytoplasmic	All tumor cells
Brachyury	Positive	Nuclear	Approximately 95% of cases
HBME-1	Positive	Cytoplasmic	Nearly all tumor cells
CK19	Positive	Cytoplasmic	Nearly all tumor cells
EMA	Positive	Cell membrane & cytoplasm	Nearly all tumor cells
S100	Positive	Nuclear & cytoplasmic	About 40-50% of tumor cells, strong but focal
34bE12	Positive	Cytoplasmic	Approximately 60% of cases
HMB-45	Positive	Cytoplasmic	Approximately 45% of cases
CEA-P	Positive	Cytoplasmic	Approximately 40% of cases
Podoplanin	Positive	Cytoplasmic	Same as D2-40; approximately 15% of cases
CK7	Positive	Cytoplasmic	Only about 10% of cases
CEA-M	Negative		
GFAP	Negative		

- Dysregulation within tyrosine kinases: Platelet-derived growth factor receptor, epidermal growth factor receptor, and downstream pathways

Electron Microscopy

- Large cells with abundant cytoplasm and variably sized vacuoles
- Mitochondria-rough endoplasmic reticulum (RER) complexes
 - Single cisternae of RER surround mitochondria
- Desmosomes, primitive cell junctions, intermediate filaments, and tonofibrils

DIFFERENTIAL DIAGNOSIS

Chondrosarcoma

- Tumor produces cartilage matrix and very rarely myxoid matrix
- No chief cells or physaliferous cells present
- **Negative:** Brachyury

Mucinous Adenocarcinoma (Primary or Metastatic)

- Salivary gland or metastatic
- Atypical epithelial cells present in glandular arrangement
- Matrix is mucinous rather than myxoid
- **Negative:** Brachyury and usually S100 protein

Chordoid Meningioma

- Rare, frequently with peritumoral lymphoid infiltrate
- Nearly always supratentorial
- Spindled, epithelioid cells with myxoid matrix
- **Positive:** EMA; **negative:** S100 protein, brachyury

Chordoid Glioma

- Benign neoplasm, involving 3rd ventricle
- **Positive:** Glial markers

Liposarcoma

- Lipoblasts have multivacuolated cells with nuclear compression
- Fat in background, which can be myxoid
- **Positive:** S100 protein; **negative:** Pan-cytokeratin, EMA, brachyury

Myoepithelioma/Myoepithelial Carcinoma

- Neoplastic cells arranged in nests, cords, and solid groups
- Varying proportions of epithelioid, spindled, plasmacytoid, and clear cells
- Cytoplasmic vacuolation is often prominent
- **Positive:** Cytokeratin, S100 protein; **negative:** Brachyury

Extraskelatal Myxoid Chondrosarcoma

- Soft tissue-based tumors, sharing histologic features, but lacking cytokeratin and brachyury

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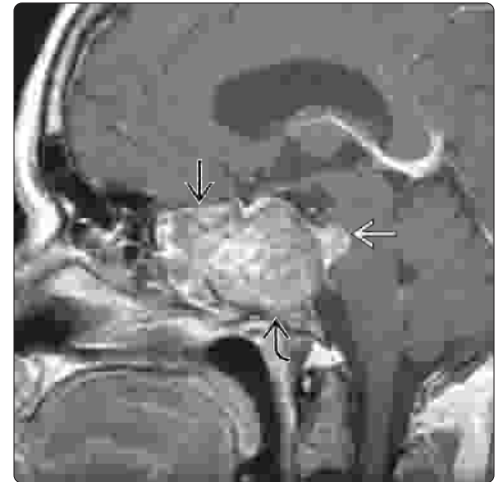
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Graphic of Expansile Destructive Mass

(Left) Sagittal graphic shows an expansile, destructive mass originating from the clivus, "thumbing" the pons [1], and elevating the pituitary gland [2]. Note bone fragments within the chordoma. (Right) Sagittal MR T1WI with contrast reveals near total replacement of the clivus by a heterogeneously enhancing, destructive mass. There is invasion into the sphenoid [3] and basiocciput [4]. The mass shows "thumbing" of the pons posteriorly [5].

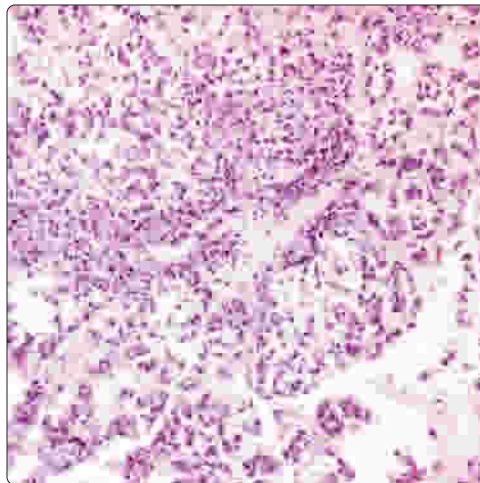


MR of Large Base of Skull Chordoma

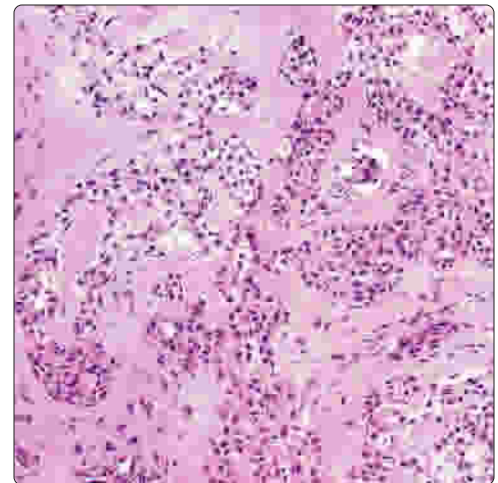


Cords and Clusters of Epithelioid Cells

(Left) There are broad sheets, clusters, and cords of neoplastic cells set within a myxoid stromal background. Bubbly cytoplasm is noted even at this power. (Right) At medium power the distribution of matrix and nests of cells can resemble a number of entities, including salivary gland tumors and metastases. There is a fibrous stroma.

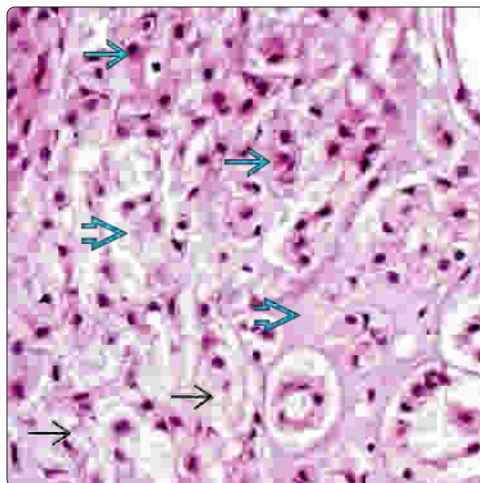


Fibrous Stroma Surrounding Tumor Nests

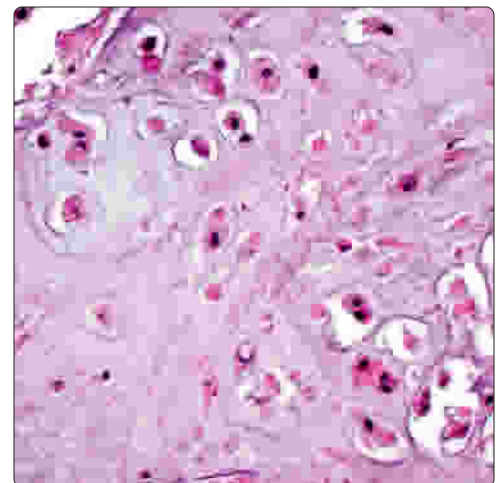


Cords in Myxoid-Mucinous Matrix

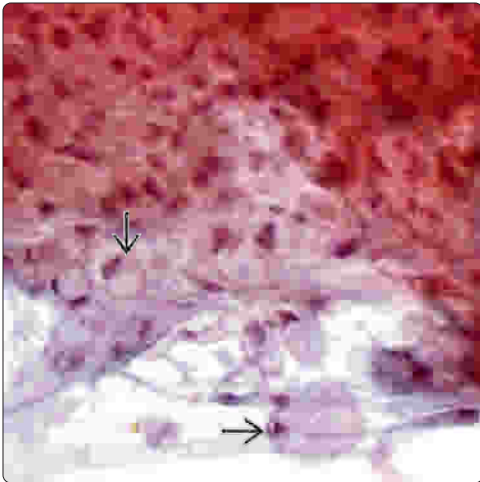
(Left) Physaliferous cells [1] are characteristic of chordoma, showing "bubbly" cytoplasm and eccentric nuclei. Short cords of epithelioid polygonal cells [2] are set in a myxoid to mucinous matrix [3]. (Right) Occasionally, foci of chordomas can have a background matrix that is solid to the point of resembling hyaline-like cartilage matrix. This is an example of a chondroid chordoma. Immunohistochemistry can be useful in separating this tumor from others in the differential.



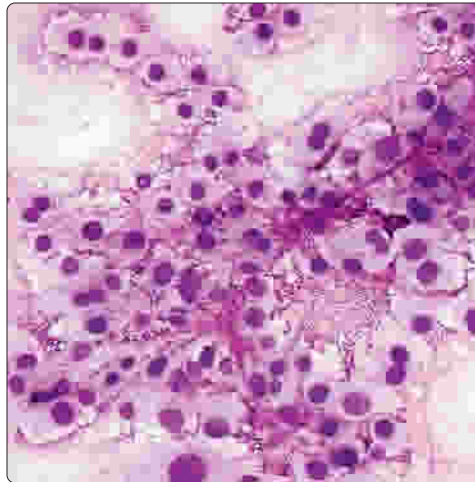
Chondroid Matrix in Chordoma




Physaliphorous Cells in FNA

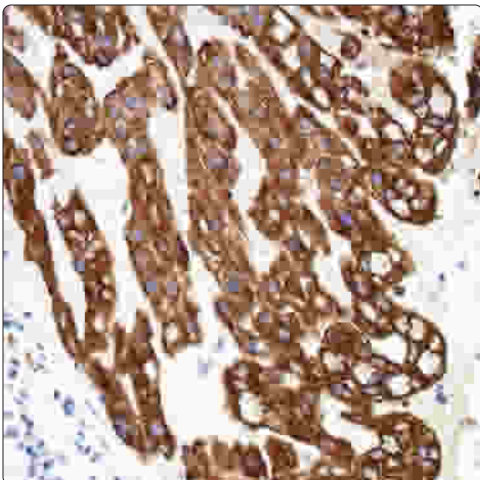


Epithelioid Cells in Cellular Smear

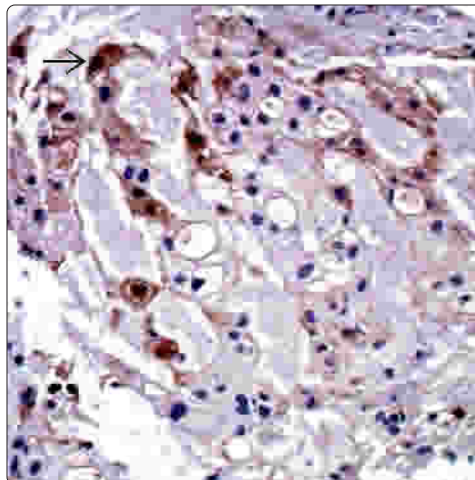



(Left) There are 2 cell types noted in chordomas, the chief cells and the physaliferous cells. Physaliferous cells  show a finely bubbled cytoplasm and are distinctive in these tumors. (Right) Fine-needle aspiration will often show cords and nests of cells with a regular polygonal shape, amphophilic cytoplasm, and nuclei with finely dispersed chromatin. The cells can be arranged around vascular cores and make definitive diagnosis difficult.

CK-PAN Highlights Neoplastic Cells

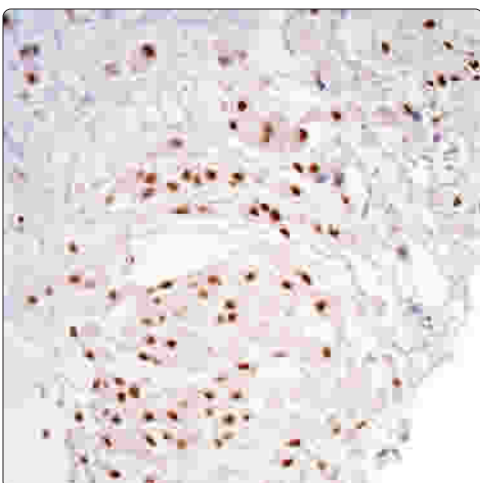


S100 Protein Within Neoplastic Cells

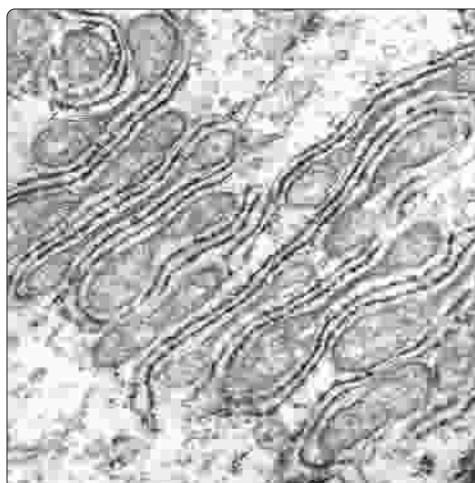


(Left) Immunohistochemistry for cytokeratin results in a strong, diffuse cytoplasmic reaction in chordoma, a reliable way to help separate chordoma from chondrosarcoma. (Right) S100 protein is usually focally, although strongly positive in the nucleus and cytoplasm  of chordoma.

Brachyury Nuclear Reaction



Electron Microscopy With Cisternae



(Left) A brachyury nuclear stain is a very helpful confirmatory study for chordoma, as no other tumors in the differential diagnosis are positive for this marker. (Right) Clusters of mitochondria are nearly completely surrounded by a single rough endoplasmic reticulum (RER) cisternae, forming a mitochondria-RER complex. This complex is quite characteristic for chordoma. Glycogen, microvilli, and intermediate filaments were present elsewhere in the cells of this case. (Courtesy S. Bhuta, MD.)

Liposarcoma

KEY FACTS

TERMINOLOGY

- Malignant neoplasm of adipose tissue (adipocytes)

CLINICAL ISSUES

- Represents up to 15-25% of all sarcomas
- ~ 3-6% of liposarcomas occur in head and neck
- Most common sites of occurrence include larynx and hypopharynx followed by neck
- Wide local surgical excision to include tumor-free margins is treatment of choice
- More aggressive surgical procedures may be indicated for higher-grade histologic variants
- 5-year survival rate for all liposarcomas of the head and neck ~ 67%

MICROSCOPIC

- WHO classification includes
 - Atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL)

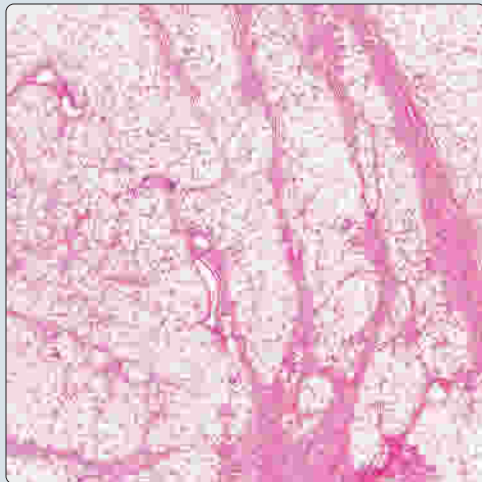
- Dedifferentiated liposarcoma
- Myxoid/round cell liposarcoma
- Pleomorphic liposarcoma

ANCILLARY TESTS

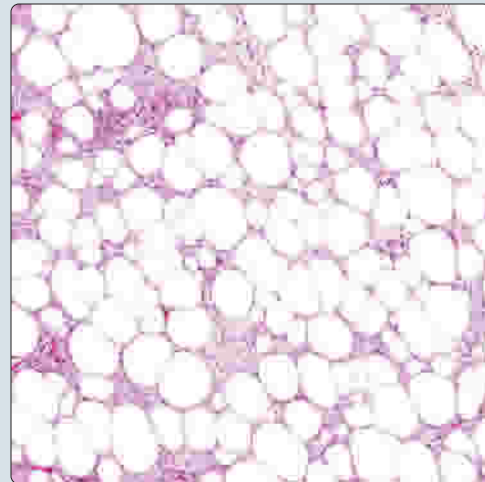
- MDM2 and CDK4 immunoreactivity
 - IHC staining for MDM2 and CDK4 detected in majority of ALT/WDL
 - Small percentage of spindle cell/pleomorphic lipoma expresses MDM2 and CDK4
 - MDM2 and CDK4 reactivity present in dedifferentiated liposarcoma
 - MDM2 and CDK4 staining in myxoid and round cell liposarcoma typically negative
- FISH for MDM2 and CDK4
 - Highly sensitive and specific
 - Superior to immunohistochemistry with small false-positive rate

Cords Separated by Fibrous Septa

(Left) Cervical neck well-differentiated (lipoma-like) liposarcoma is characterized by an unencapsulated adipose cell proliferation composed of cords and nests of adipocytes separated by fibrous septa. At low magnification, there are no overt features indicative of malignancy, and the findings resemble a lipoma. (Right) At higher magnification, the features still suggest a diagnosis of a lipoma except that there is greater variation in the size and shape of the adipocytes, as would be expected in a lipoma.

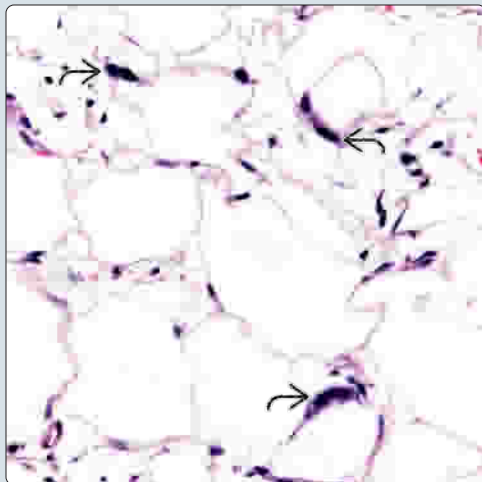


Variation in Adipocyte Size and Shape

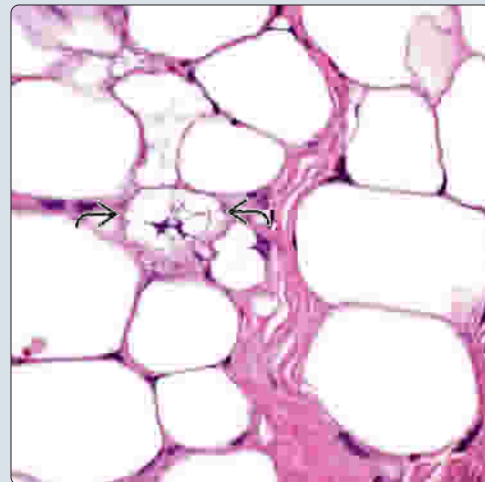


Nuclear Pleomorphism and Hyperchromasia

(Left) In addition to variation in size and shape of adipocytes, there are also adipocytes showing nuclear pleomorphism and hyperchromasia [arrow], findings present in well-differentiated liposarcoma. (Right) Lipoblasts [arrow] are characterized by hyperchromatic nuclei that appear indented or scalloped that may be centrally or peripherally located in the cell. Their importance has been overemphasized in the diagnosis, and they tend to be few in number in well-differentiated liposarcoma.



Lipoblast



TERMINOLOGY

Definitions

- Malignant neoplasm of adipose tissue (adipocytes)

ETIOLOGY/PATHOGENESIS

Idiopathic

- No known associated etiologic factors
- Arise de novo
 - Rarely may originate from preexisting lipoma

Histogenesis

- Arise from primitive mesenchymal cells rather than mature adipose tissue
 - Accounts for occurrence in areas relatively devoid of fat (i.e., mucosal sites of head and neck)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Represent up to 15-25% of all sarcomas
 - ~ 3-6% of liposarcomas occur in head and neck
- Age
 - Laryngeal and hypopharyngeal liposarcoma
 - Occurs over wide age range but most common in 6th and 7th decades of life
 - Neck liposarcomas
 - Occur over wide age range, usually at younger ages (~ decade younger) than non-head and neck liposarcomas
- Sex
 - For laryngeal and hypopharyngeal liposarcoma
 - Male > female
 - Neck liposarcomas
 - Equal gender distribution

Site

- In head and neck, most common sites of occurrence include larynx and hypopharynx followed by neck

Presentation

- Symptoms vary per site of involvement and tumor size
 - Larynx
 - Hoarseness, dysphonia, dysphagia, airway obstruction
 - Pharynx
 - Dysphagia, airway obstruction
 - Neck
 - Slowly growing painless mass

Treatment

- Surgical approaches
 - Wide local surgical excision to include tumor-free margins is treatment of choice
 - More aggressive surgical procedures may be indicated for higher-grade histologic variants
- Radiation
 - Utility of radiotherapy remains controversial
 - Evidence supports use of postoperative radiotherapy as adjunct to surgery in cases where
 - Tumor cannot be completely resected

- Tumor is close to surgical margins

Prognosis

- Recurrence common
 - In particular for well-differentiated liposarcomas (WDL) that initially may be diagnosed as lipoma
 - Molecular testing for relapsing lipomas may assist in diagnosing by presence of *MDM2/CPM* amplification
 - Generally occurs within 3 years following initial treatment
 - Usually is of same histology as primary tumor
 - May rarely dedifferentiate
 - Histologic appearance less differentiated
 - Associated with more aggressive biology than primary (differentiated) tumor
- Nodal metastasis rare
 - Neck dissection generally not indicated
- Distant metastasis may occur
 - More common with higher-grade histologic variants
 - Metastases occur to lungs, bone, liver
- 5-year survival rate for all liposarcomas of head and neck ~ 67%
 - Influenced by histologic type
 - 5-year survival rate
 - All head and neck liposarcomas ~ 67%
 - WDL: 85-100%
 - Myxoid liposarcoma: 71-95%
 - Round cell liposarcoma: 12.5-55.0%
 - Pleomorphic liposarcoma: 45%
- In addition to histologic type, other important prognostic factors include
 - Size of tumor
 - Location of tumor
 - Laryngeal/hypopharyngeal, facial tumors have best prognosis
 - Oral and pharyngeal tumors have worst prognosis
 - Controversy exists as to issue of multicentric liposarcomas vs. metastatic liposarcoma
 - Presence of clonality in multifocal myxoid liposarcoma supportive of metastasis rather than multifocal tumor

MACROSCOPIC

General Features

- Circumscribed &/or encapsulated, lobulated mass
- Vary in appearance from yellow to tan-white in color
 - Myxoid or gelatinous appearance

Size

- Can attain very large sizes, especially relative to soft tissue sites (e.g., neck)
- Mucosal-based lesions rarely exceed 10 cm and generally measure < 5 cm in greatest dimension

MICROSCOPIC

Histologic Features

- WHO classification includes
 - Atypical lipomatous tumor (ALT)/WDL
 - Dedifferentiated liposarcoma
 - Myxoid/round cell liposarcoma
 - Pleomorphic liposarcoma

Atypical Lipomatous Tumor/Well-Differentiated Liposarcoma

- Most common morphologic type (30-40%) in late adult life, most common morphologic type in relationship to upper aerodigestive tract liposarcomas
- Often diagnosed as lipoma due to bland histology, but following 1 or more recurrences will diagnosis of liposarcoma then be considered
- Histologically resembles lipoma except for greater variation in size and shape of adipocytes
 - Greater variation in size and shape of adipocytes
 - Presence of scattered lipoblasts (absence of lipoblasts does not preclude diagnosis)
 - Absence of encapsulation
- Terms atypical lipoma or atypical lipomatous tumor have been utilized for superficial (cutaneous or subcutaneous) lipogenic tumors with histologic appearance of WDL, which have tendency to recur
 - Use of this terminology should be viewed with caution in those WDL occurring in more vital areas (deep neck, nasopharynx, sinonasal cavity, larynx, and hypopharynx) where inadequate excision and subsequent recurrence may result in increased morbidity and mortality
 - Use of WDL rather than atypical lipoma should convey to surgeon that neoplasm requires complete resection in most conservative manner to assure tumor-free margins and not just simple excision
- **Spindle cell liposarcoma**
 - Considered to represent rare atypical/low-grade malignant lipogenic neoplasm regarded as variant of atypical lipomatous tumor
 - Tends to occur in subcutaneous tissue of extremities, trunk and head, and neck region
 - Histologically, variably cellular neoplasm composed of atypical lipogenic cells showing variations in size and shape and spindled tumor cells with slightly enlarged, often hyperchromatic nuclei
 - Multivacuolated lipoblasts may be present
 - Focal myxoid stromal changes may be present
 - Immunohistochemically: CD34 at least focally positive; only scattered cells in limited cases may show nuclear expression of MDM2
 - FISH analysis negative for MDM2/CDK4 amplification
 - Based on clinicopathologic and molecular findings, may represent atypical/low-grade counterpart of spindle cell lipoma rather than morphologic variant of ALT/WDL

Dedifferentiated Liposarcoma

- Histologic progression of ALT/WDL to higher grade, less well-differentiated neoplasm in primary (de novo) neoplasm (90%) and recurrent neoplasm (10%)
 - High-grade component usually is nonlipogenic and only rarely is lipogenic
 - Accounts for 18% of all liposarcomas
 - Most common site of occurrence is retroperitoneum > > > extremities; < 20% occur in head and neck (and other) sites
 - Histologically, in ~ 90%, dedifferentiated component has appearance of high-grade fibrosarcoma or undifferentiated pleomorphic sarcoma
 - Displays range of subtypes including

- Storiform-pleomorphic and myxoid forms (most common)
- Giant cell and inflammatory forms (less common)
- In ~ 10%, may resemble low-grade fibrosarcoma or fibromatosis

Myxoid/Round Cell Liposarcoma

- Continuum of lesions that include differentiated myxoid tumors with lipoblastic differentiation to poorly differentiated round cell tumors with inconspicuous lipoblastic differentiation
- Represents 1/3 to 1/2 of all liposarcomas
- Represents poorly differentiated form of myxoid liposarcoma
- Characterized by presence of
 - Densely cellular solid sheets of back-to-back primitive round cells with hyperchromatic nuclei, prominent nucleoli, increased nuclear:cytoplasmic ratio, granular- to vacuolated-appearing cytoplasm
 - Increased mitotic activity as well as necrosis and hemorrhage are present
 - Sparse to absent intervening myxoid, fibrillar, or myxomucinous stroma
 - Vascular pattern present but generally compressed by cellular proliferation
 - Presence of transitional areas from myxoid to hypercellular round cell supports contention that myxoid and round cell liposarcomas represent histological continuum of myxoid liposarcoma
 - Notion that myxoid and round cell liposarcoma represent histological continuum further supported by presence of shared chromosomal aberrations
- Occurs in younger age group than ALT/WDL and dedifferentiated liposarcoma: Peak incidence in 5th decade
- Most common in lower extremity (75% of cases): Medial thigh > popliteal area; less commonly occurs in retroperitoneum, rare in head and neck
- Myxoid liposarcoma is histologically characterized by
 - Lobular or nodular growth
 - Uniform round to oval-shaped mesenchymal (nonlipogenic appearing) cells
 - Variable numbers of signet ring lipoblasts are present
 - Usually readily identifiable; may be most prominent at periphery of nodules
 - Prominent myxoid stroma rich in glycosaminoglycans or hyaluronidase-sensitive acid
 - Delicate plexiform capillary vascular pattern present, representing an important diagnostic clue; assists in differentiating from benign tumors (e.g., myxoma, others)
 - Cellular component typically lacks nuclear pleomorphism, significant mitotic activity, or tumor giant cells
 - Extracellular mucin pools or lakes creating lymphangioma-like appearance can be identified
 - Cartilaginous, osseous, leiomyomatous differentiation may occur; rarely, rhabdomyosarcomatous differentiation may be present
- Round cell liposarcoma represents poorly differentiated form of myxoid liposarcoma characterized by

- o Densely cellular proliferation solid sheets of back-to-back primitive round cells with hyperchromatic nuclei, prominent nucleoli, increased nuclear:cytoplasmic ratio, and granular- to vacuolated-appearing cytoplasm
- o Increased mitotic activity, necrosis, and hemorrhage are present
- o Sparse to absent intervening myxoid, fibrillar, or myxomucinous stroma
- o Plexiform capillary vascular pattern present but generally compressed by cellular proliferation
- o Presence of transitional areas from myxoid to hypercellular round cell supports contention that myxoid and round cell liposarcomas represent histological continuum of myxoid liposarcomas
- o Further support of this consideration is presence of shared chromosomal aberrations

Pleomorphic Liposarcoma

- High-grade sarcoma composed of
 - o Variable numbers of pleomorphic lipoblasts characterized by spindle and giant cells with 1 or more enlarged hyperchromatic nuclei scalloped by cytoplasmic vacuoles
 - Cytoplasmic vacuoles containing lipid droplets
 - o Fascicles of spindle-shaped cells and smaller, round cells admixed with multinucleated giant cells resembling such tumors as undifferentiated pleomorphic sarcoma, as well as pleomorphic lipoblasts
 - Limited lipoblastic features may be present
 - o Prominent cytoplasmic eosinophilia may be present and, in presence of limited lipoblastic findings, may suggest diagnosis of rhabdomyosarcoma
 - o Extra- and intracellular eosinophilic hyaline globules may be identified and likely represent lysosomal structures
 - o Tumor necrosis present
 - o Absence of areas of ALT/WDL or other line of differentiation
- Epithelioid variant of pleomorphic liposarcoma
 - o Predominantly composed of solid, cohesive sheets and clusters of epithelioid cells with round to oval nuclei, prominent nucleoli, eosinophilic cytoplasm, and distinct cell borders
 - o Lipogenic differentiation in form of pleomorphic lipoblasts focally present
 - o Often associated with higher mitotic rate than seen in association with pleomorphic (nonepithelioid) liposarcoma
 - o Tumor necrosis present

Mixed-Type Liposarcoma

- Extremely rare, representing ~ 5% (or less) of all liposarcomas
- Primarily occurs in retroperitoneum
- Histologically defined by presence of combined
 - o Classic WDL associated with classic pleomorphic liposarcoma
 - o ALT/WDL with myxoid/round cell and WDL/dedifferentiated liposarcoma
 - o Myxoid/round cell and pleomorphic liposarcoma
- Molecular testing has allowed for classification of some of these mixed-type liposarcomas within 1 neoplasm within current WHO classification

General Histologic Features

- Lipoblasts are neoplastic cells that recapitulate differentiation cascade of normal fat
 - o Classic appearing lipoblasts have
 - Hyperchromatic indented or scalloped nucleus
 - Lipid-rich droplets in cytoplasm
 - Nucleus either centrally or peripherally located in cell
 - o Importance is overemphasized
 - Few are present in ALT/WDL
 - o Pattern and cellular components are more important
 - o Simulators of lipoblasts include
 - Reactive changes (fat necrosis, atrophy, foreign body reaction)
 - Fixation artifact or signet ring cells in other neoplasms
- Mitoses, necrosis, and hemorrhage can be identified in all histologic variants
 - o Generally correlate to amount of cellular pleomorphism
 - o Mitoses are particularly prominent in pleomorphic variant

ANCILLARY TESTS

Cytology

- Smears may include mixture of mature-appearing fat traversed by bands of fibrous collagen and vessels
- Nuclei within fat and fibrous bands mildly irregular, hyperchromatic, and enlarged, with 1 or 2 small nucleoli
- Infrequently, lipoblasts may be identified

Histochemistry

- Prominent myxoid stroma rich in
 - o Glycosaminoglycans or hyaluronidase-sensitive acid
 - o Mucopolysaccharides
- In general, special stains are of little if any assistance in diagnosis

Immunohistochemistry

- Adipocytes and lipoblasts
 - o Variable S100 protein immunoreactivity
 - o Vimentin (+)
 - o All other markers essentially negative
- MDM2 and CDK4 immunoreactivity and FISH
 - o IHC staining for MDM2 and CDK4 detected in majority of ALT/WDL
 - Nuclear staining
 - Reasonable 1st tool in diagnosis
 - o FISH
 - Highly sensitive and specific
 - Superior to immunohistochemistry with small false-positive rate
 - Absent in lipomas
 - Small percentage of spindle cells/pleomorphic lipomas expresses MDM2 and CDK4
 - MDM2 and CDK4 reactivity present in dedifferentiated liposarcoma
 - MDM2 and CDK4 staining in myxoid and round cell liposarcoma typically negative

Genetic Testing

- ALT/WDL, dedifferentiated LPS characterized by 12q13-15 region amplification

- Characterized by giant marker and ring chromosomes
 - Contains amplified sequences 12q13-15, site of several genes (*MDM2*, *CDK4*, others)
 - *MDM2* (and *HMGA2*) consistently amplified
 - *CDK4* coamplified in ~ 90%
- Molecular event not reported in benign lipomas
- Dedifferentiated liposarcoma
 - Shares similar findings as ALT/WDL, although displays more extensive chromosomal abnormalities
 - 12q13-15 amplifications more complex than in ALN/WDL
- Myxoid and round cell liposarcoma
 - Characterized by reciprocal t(12;16)(q13;p11) translocation
 - Present in > 90% of cases
 - Results in fusion of the *DDIT3* gene on chromosome 12 with *FUS* gene on chromosome 16
 - Presence of *FUS/DDIT3* fusion sensitive and specific for myxoid liposarcoma
 - Chimeric *FUS-DDIT3* gene results in 3 fusion transcripts: Type II identified in most myxoid/round cell liposarcomas
- Pleomorphic liposarcoma
 - Various chromosomal gains and losses
 - Dysregulation of several tumor suppressor pathways common
 - No amplification of 12q14-15 region
- Indications for IHC &/or molecular analysis for lipomatous tumors include
 - Presence of equivocal cytologic atypia
 - Recurrent lipomas
 - Deep-seated tumors without cytologic atypia > 15 cm
 - Retroperitoneal or intraabdominal tumors without cytologic atypia

DIFFERENTIAL DIAGNOSIS

Lipoma

- Typically encapsulated
- Lipoblasts not present
- Majority negative for MDM2 and CDK4

Other Sarcomas

- Potentially overlapping histologic features, especially in higher grade sarcomas
- May have lipoblastic-appearing cells
- Unique immunohistochemical &/or cytogenetics relative to some sarcomas (e.g., rhabdomyosarcoma, leiomyosarcoma, synovial sarcoma)
- Typically negative for MDM2 and CDK4 by FISH

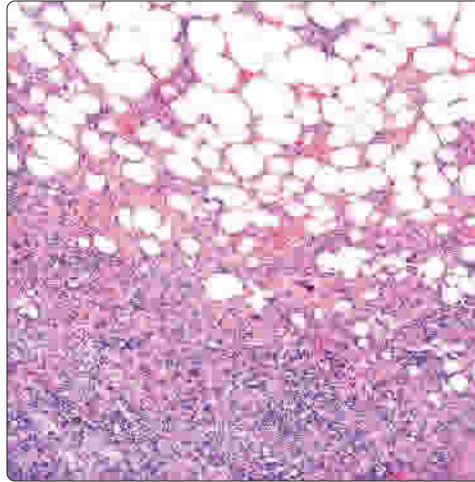
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Imaging Findings in Well-Differentiated Liposarcoma

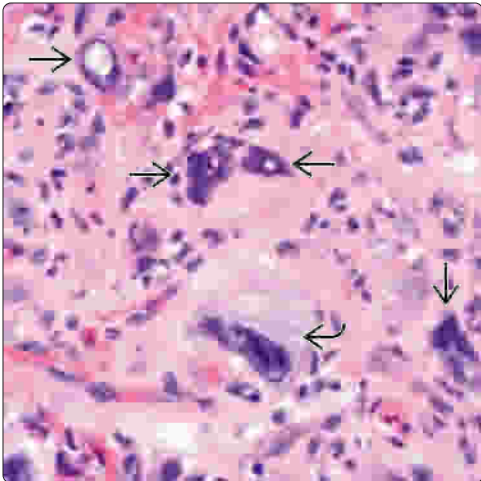


Transition From ALN/WDL to DL

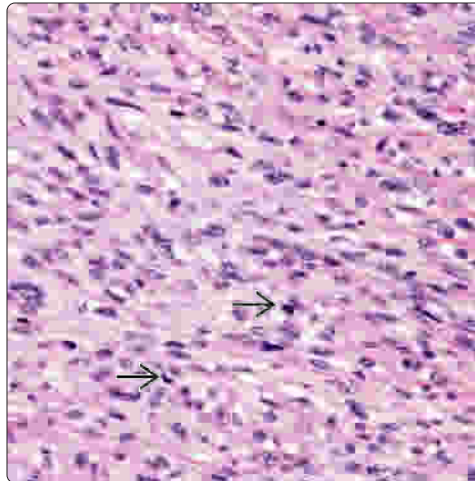


(Left) CT demonstrates a typical head and neck liposarcoma in the right posterior cervical space in which the mass is predominantly composed of fat with diffuse thin stranding throughout the tumor matrix. (Right) Cervical neck dedifferentiated liposarcoma (DL) shows transition or interface between atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL) (top 1/2) and dedifferentiated zone (bottom 1/2).

Nonlipogenic Appearing Cells

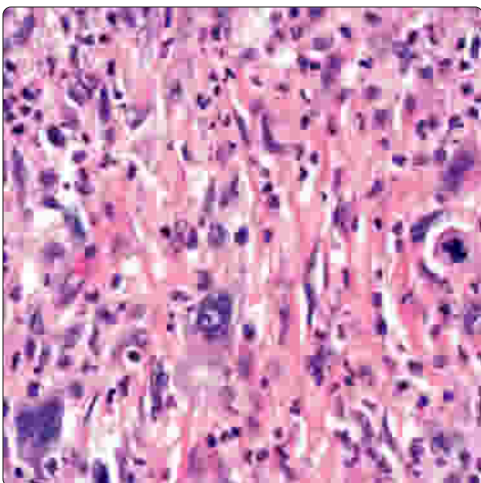


High-Grade Sarcoma Features

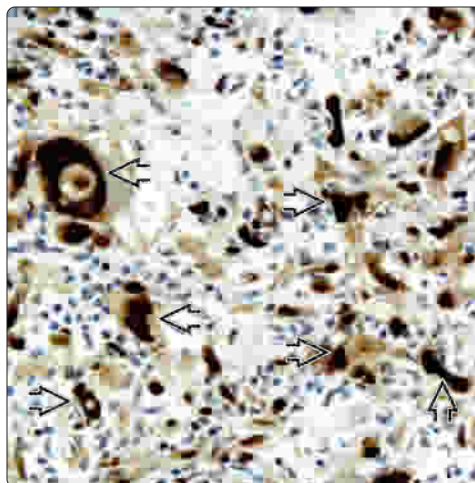


(Left) Dedifferentiated liposarcoma is shown in which the high-grade component typically features nonlipogenic-appearing cells with only a limited cellular component, with features suggesting lipogenic derivation. (Right) Dedifferentiated liposarcoma shows histologically high-grade sarcoma, including increased mitotic figures characterized similarly to nonlipogenic sarcomas. In ~90%, the dedifferentiated component looks like high-grade fibrosarcoma.

Features Similar to Undifferentiated Pleomorphic Sarcoma



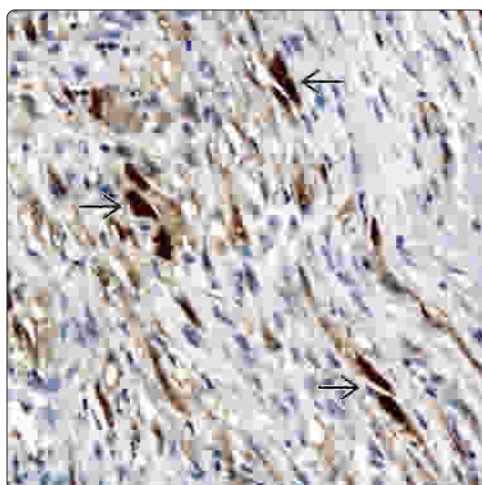
MDM2 Expression in Dedifferentiated Liposarcoma



(Left) Dedifferentiated liposarcomas may be suggestive of an undifferentiated pleomorphic sarcoma (UPS). A histologic hallmark (not shown) would be transition either in primary or recurrent tumor from well-differentiated liposarcoma to nonlipogenic sarcoma. (Right) When confronted with a high-grade undifferentiated malignant neoplasm ± sarcomatous features, the presence of strong nuclear reactivity for MDM2 is evident.

CDK4 Expression in Dedifferentiated Liposarcoma

(Left) Nuclear reactivity for CDK4 supports a diagnosis of dedifferentiated liposarcoma and aids in differentiation from other high-grade malignant neoplasms. (Right) Enhanced CT shows a well-circumscribed retropharyngeal mass with nodular enhancement on the right and primarily fatty density on the left. The mass protrudes anteriorly into the submandibular space, elevating the submandibular gland. The anterolateral margin of the enhancing nodule shows invasive growth.

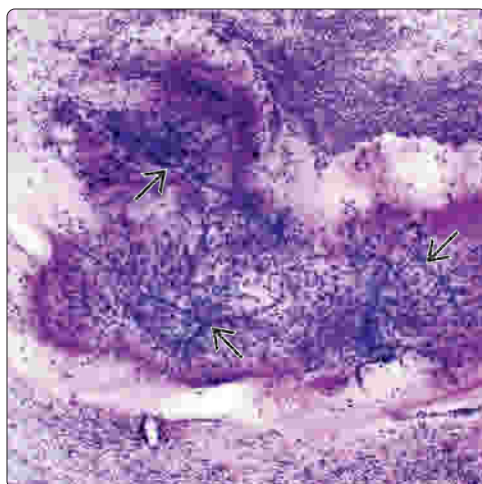


Imaging Findings in Myxoid Liposarcoma

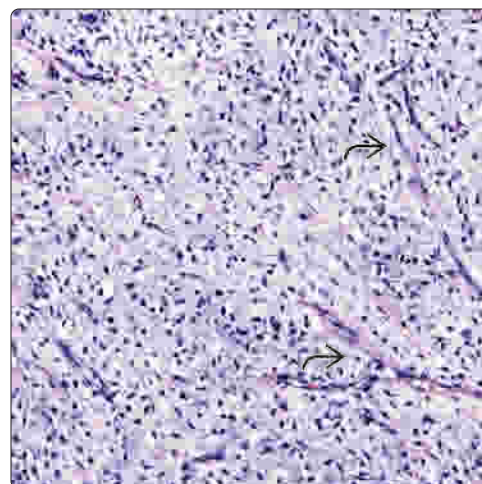


Myxoid Liposarcoma, Fine-Needle Aspiration Biopsy

(Left) Fine-needle aspiration biopsy shows a cellular smear with delicately arborizing vascular plexus, a feature seen in myxoid liposarcoma. (Right) Variably cellular myxoid lesion is shown with a plexiform capillary pattern characterized by a delicate arborizing (capillary-like) pattern. This vascular pattern is not typically present in reactive &/or benign lesions.

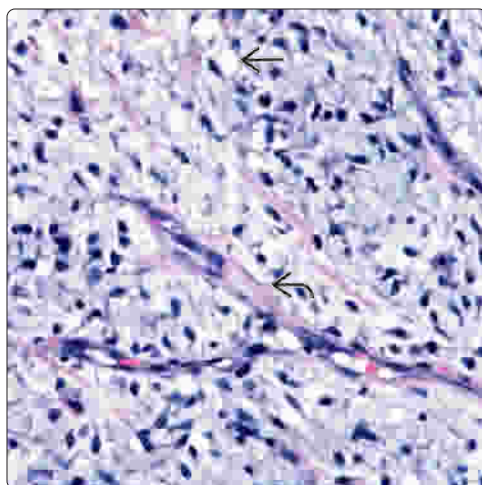


Myxoid Stroma and Arborizing Vascularity

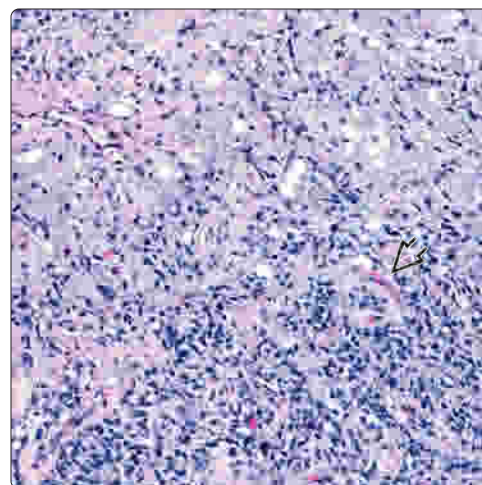


Plexiform Capillary Pattern

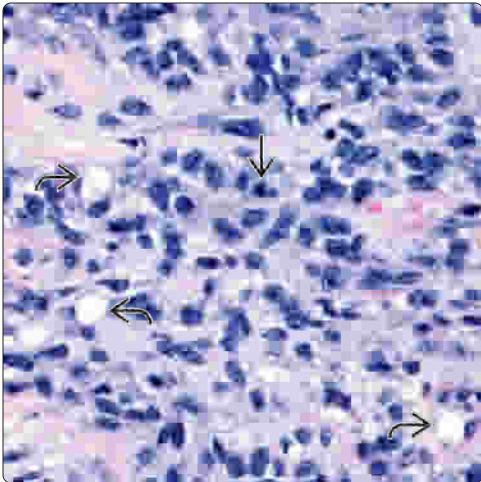
(Left) Plexiform capillary pattern vascularity with an arborizing pattern is a feature seen in several types of sarcomas, including myxoid liposarcoma. Lipoblasts in varying stages of development, including signet ring forms, are present. (Right) Shown is myxoid liposarcoma (top) transitioning to cellular round cell liposarcoma (bottom), which represents a poorly differentiated form of myxoid liposarcoma. A vascular pattern is compressed by the cellular proliferation.



Transitional Area



Primitive Round Cells

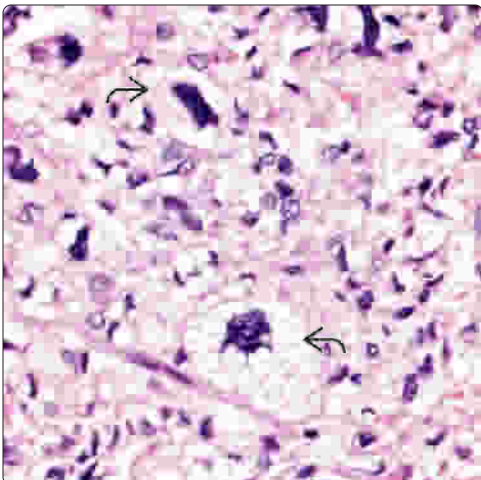


Markedly Pleomorphic Cells

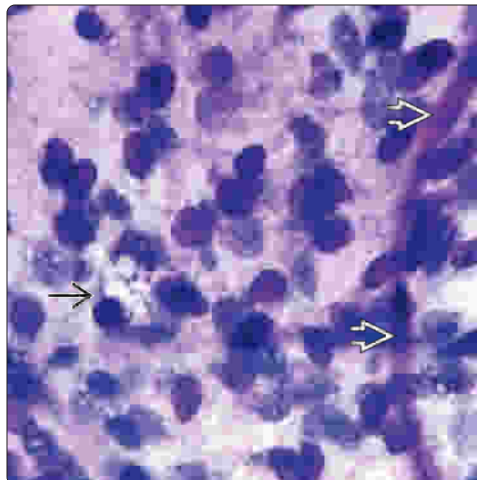


(Left) Round cell liposarcoma is characterized by densely cellular solid sheets of primitive round cells with hyperchromatic nuclei, prominent nucleoli, and granular- to vacuolated-appearing cytoplasm [1]. Increased mitotic activity is seen [2]. (Right) Pleomorphic liposarcoma is a hypercellular lesion composed of spindle-shaped cells with vacuolated cytoplasm as well as cells with markedly pleomorphic and hyperchromatic nuclei [3].

Multivacuolated Lipoblasts

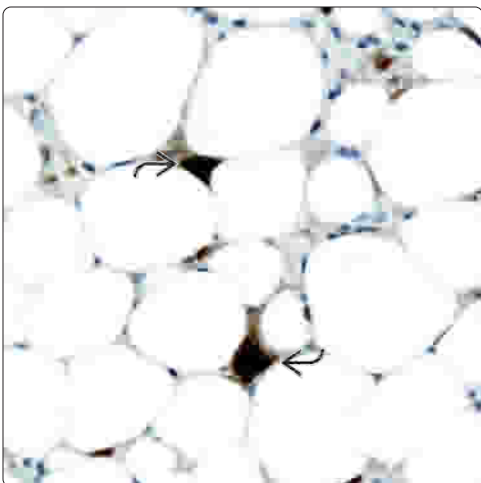


Fine-Needle Aspiration of Well-Differentiated Liposarcoma

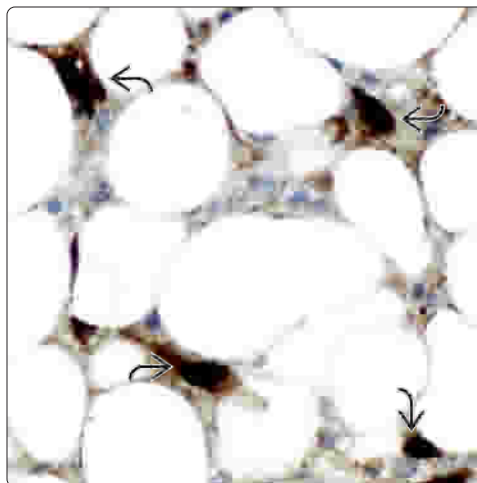


(Left) Multivacuolated lipoblasts [4] are characterized by 1 (or more) enlarged hyperchromatic nuclei scalloped by cytoplasmic vacuoles. Pleomorphic liposarcoma resembles other sarcomas, but the presence of lipoblasts is a differentiating finding supporting the diagnosis. (Right) A lipoblast [5] is identified within a very cellular smear taken from the anterior neck region. There is compression of the nucleus by a multivacuolated cytoplasm. Note the capillary [6] within the proliferation.

MDM2 Expression in Well-Differentiated Liposarcoma



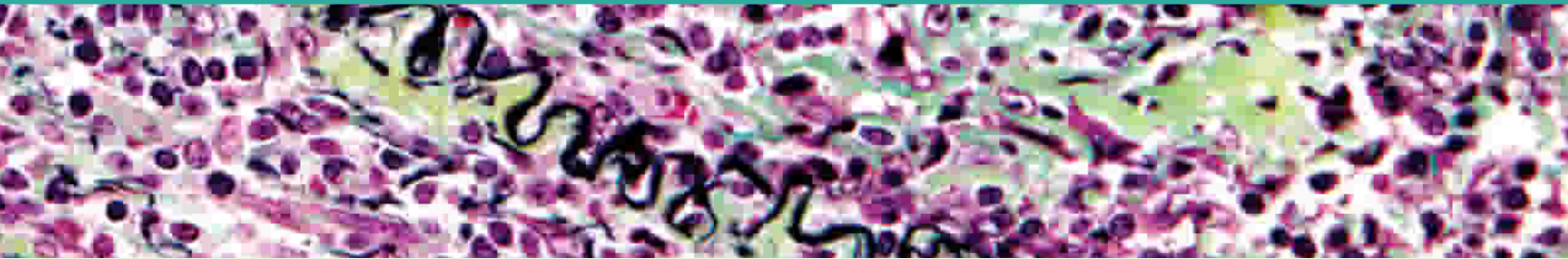
CDK4 Expression in Well-Differentiated Liposarcoma



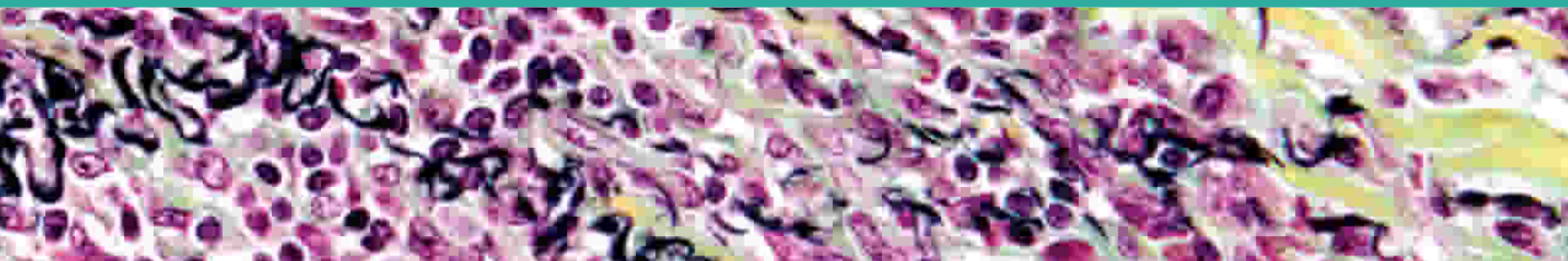
(Left) MDM2 nuclear immunoreactivity [7] is shown. (Right) CDK4 nuclear immunoreactivity [8] is shown. MDM2 and CDK4 expressions represent important markers in the diagnosis of well-differentiated liposarcoma detected in a majority of such neoplasms. FISH analysis (not shown) is more sensitive and specific compared with immunohistochemical staining with small false-positive rates and absence in lipomas.

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MACROSCOPIC

Macroscopic Anatomy

- H-shaped endocrine organ (15-25 g) composed of 2 lateral lobes (each ~ 5 cm long, 2.5 cm wide, 2 cm deep) connected by central isthmus
 - Located anterior to upper trachea, just below laryngeal cricoid cartilage
 - Lobes have pointed superior and blunt inferior poles
 - 40% of people have pyramidal lobe, which extends cephalad from isthmus
 - Size varies with stature, age, sex, iodine intake, hormonal status, and gland functional status
- Invested by delicate fibrous connective tissue that extends into gland dividing it into lobules (thyromeres)
- Cut surface is red-brown and firm; nodules seen in 10% of nongoitrous euthyroid individuals
- Paired superior and inferior parathyroid glands are attached to posterior thyroid capsule
- Small lymph nodes can be seen around isthmus, including pretracheal (Delphian) lymph node
- Embryologically derived from median anlage and 2 lateral anlagen
- **Median** anlage derived from 1st and 2nd branchial pouch endoderm at base of primitive pharynx during 4th week
 - Descends into neck, passing anterior to hyoid bone and larynx
 - Remains connected to foramen cecum by thyroglossal duct, which subsequently involutes
 - Failure of duct to involute can result in thyroglossal duct cysts
- **Lateral** anlagen (ultimobranchial bodies) derive from 4th and 5th branchial pouches during 7th week and yield C cells
 - Ultimobranchial bodies give rise to C cells, which disperse throughout mid to upper 1/3 of lateral thyroid lobes
 - Ultimobranchial body remnants, so-called solid cell nests, can be seen in lateral lobes of most thyroids

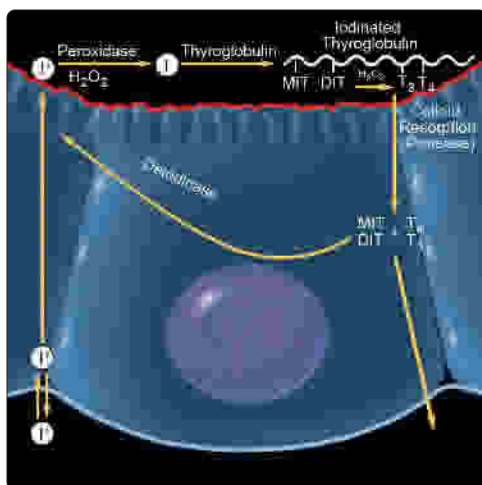
MICROSCOPIC

Microscopic Anatomy

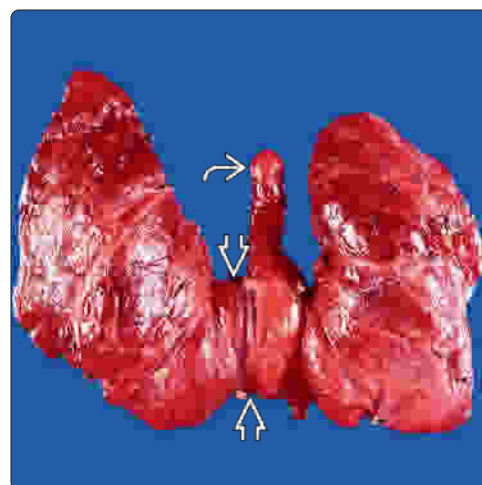
- Functional unit of thyroid gland is follicle
- Follicles are spherical, cyst-like structures of variable size (0.2-1 mm on average) and shape
 - Follicles surrounded by extensive capillary network
- Lined by monolayer of flat to columnar follicular epithelial cells (thyrocytes)
 - Cell size varies by functional status of follicle; flat cells are inactive, cuboidal cells secrete colloid, and columnar cells resorb colloid
- Colloid is eosinophilic to basophilic secretion composed mostly of thyroglobulin
 - Thyroglobulin is iodinated glycoprotein and serves as inactive storage form of active thyroid hormones T₃ and T₄
 - Resorption vacuoles are present in follicles resorbing colloid
 - Calcium oxalate crystals are often present in colloid
- Sanderson polsters are small aggregates of follicles at 1 end of follicle that may have papillary or undulating appearance
 - Seen in normal thyroids but increased in hyperplastic conditions
- Focal areas of stromal adipose tissue can be seen in normal thyroids
- Intrathyroidal skeletal muscle, cartilage, parathyroid glands, thymic tissue are occasionally present
- Parafollicular C cells account for small proportion of thyroid mass
 - Restricted to mid and superior lateral lobes
 - Located between follicular cells and basement membrane
 - Cuboidal cells with pale to blue granular cytoplasm with coarse nuclear chromatin; secrete calcitonin

Graphic of Thyroid Hormone Synthesis

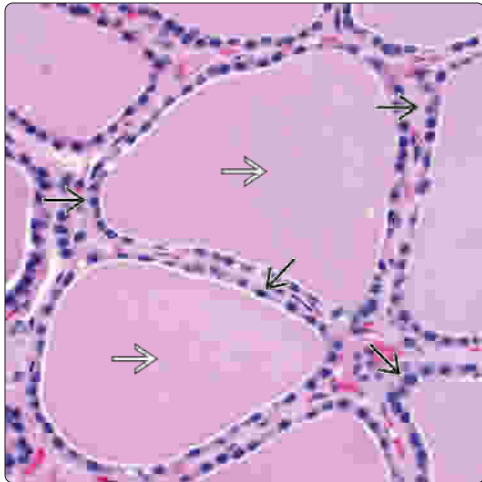
(Left) Colloid consists mostly of thyroglobulin, an iodinated glycoprotein that serves as the storage form of the active thyroid hormones T₃ and T₄. In response to pituitary TSH, follicular cells resorb thyroglobulin and convert it to T₃ and T₄, which are released into the perifollicular capillaries. (Right) Normal thyroid gland is composed of 2 lateral lobes connected by a central isthmus and invested by a thin fibrous capsule with numerous small surface vessels. 40% of thyroid glands will have a pyramidal lobe.



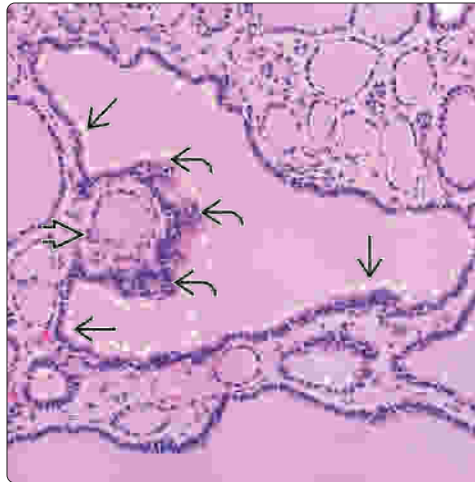
Gross of Thyroid Gland Anatomy



Follicular Epithelial Cells

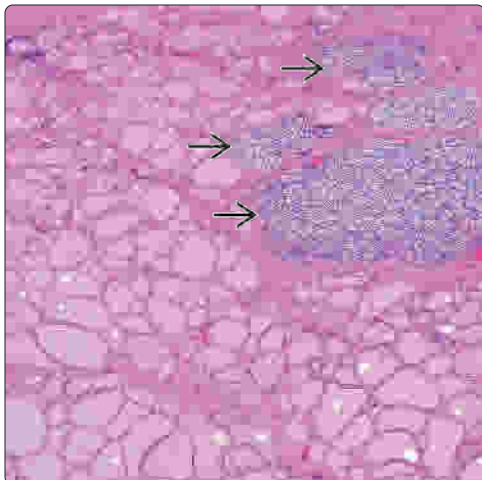


Sanderson Polster

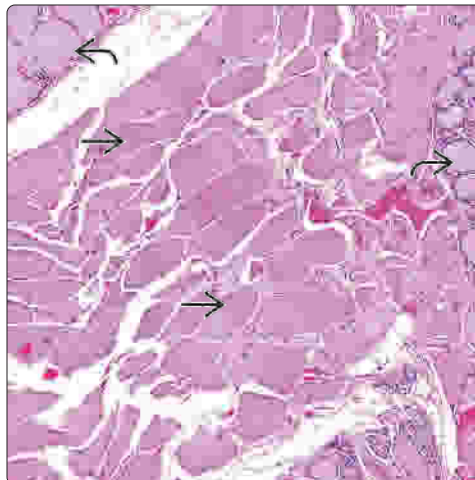


(Left) Follicles are lined by a monolayer of follicular cells surrounding a mass of colloid. Cuboidal follicular cells synthesize colloid. Flat follicular cells are inactive. (Right) Sanderson polsters are intraluminal collections of follicles at 1 end of a larger follicle and often have an undulating or papillary appearance. They are more common in active follicles, as evidenced by the resorption vacuoles.

Intrathyroidal Parathyroid Tissue

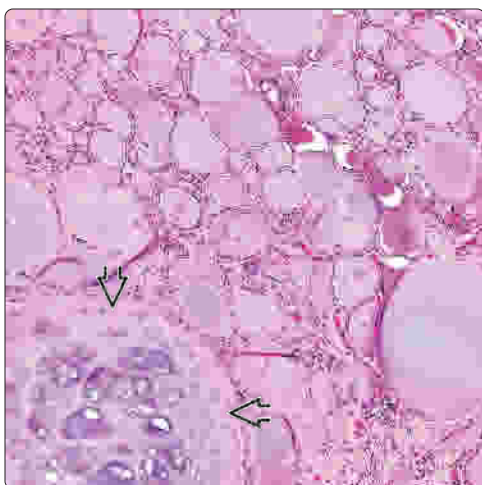


Intrathyroidal Skeletal Muscle



(Left) Intracapsular &/or intrathyroidal parathyroid tissue or glands are not uncommonly seen in otherwise normal thyroid glands. (Right) Intrathyroidal skeletal muscle is common in the isthmus region. Follicles can also be seen in extrathyroidal skeletal muscle.

Heterotopic Cartilage



Colloid Calcium Oxalate Crystals



(Left) Intrathyroidal islands of heterotopic mature hyaline cartilage, presumably of branchial pouch derivation, can be seen in the stroma in ~ 10% of thyroid glands. (Right) Irregular, rhomboidal, anisotropic calcium oxalate crystals can be seen within the colloid of most (~ 85% in autopsy studies) thyroid glands. They can be present in normal follicles but are more frequent with age, in renal failure patients on dialysis, and in inactive follicles. They are uncommon in cases of chronic thyroiditis.

Thyroglossal Duct Cyst

KEY FACTS

TERMINOLOGY

- Persistence and cystic dilatation of thyroglossal duct in midline of neck

CLINICAL ISSUES

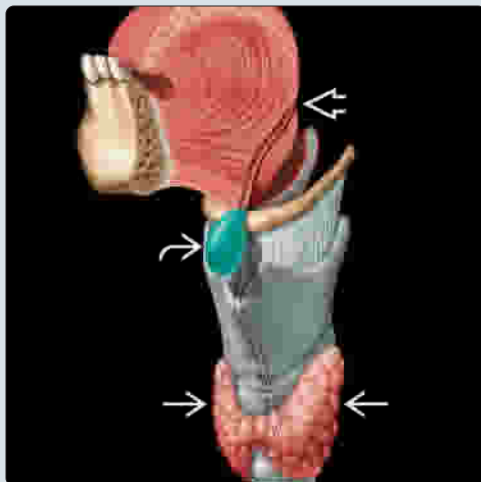
- Occurs over wide age range but majority occur prior to 4th decade of life
- Majority (~75%) occur in midline neck at or just below level of hyoid bone
 - Nearly always connected to hyoid bone
 - Uncommonly may occur lateral to midline
- Asymptomatic midline neck mass
- Adequate surgery results in cure with low, if any, recurrence(s)
 - Surgery (Sistrunk procedure) is treatment of choice
 - En bloc surgical resection of cyst
 - Middle 1/3 of hyoid bone
 - Suprahyoid tract up to foramen cecum (at base of tongue)

MICROSCOPIC

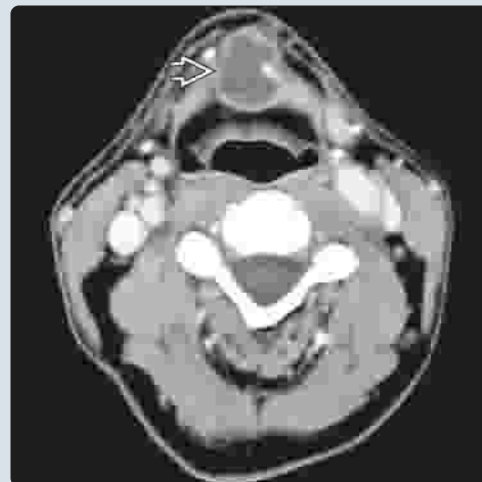
- In noninflamed cyst, lining is
 - Respiratory (columnar) epithelium, may include cilia, nondescript cuboidal epithelium, or squamous epithelium
- In presence of inflammation, cyst lining may undergo squamous metaplasia
- Presence of thyroid tissue in cyst wall varies
 - May be dependent on extent of specimen sampling
 - Generally, thyroid tissue found in > 50% of cases
- Development of carcinoma in thyroglossal duct cyst is rare
 - Majority are papillary thyroid carcinomas
 - Can be diagnosed by fine-needle aspiration
 - Diagnosis based on constellation of nuclear alterations including enlargement and elongation, variation in size and shape, clear to dispersed (very fine) appearing nuclear chromatin, nuclear crowding and overlapping, nuclear grooves, intranuclear inclusions

Thyroglossal Duct Cyst Development

(Left) From the foramen cecum at the base of the tongue, the thyroglossal duct descends in a midline caudad direction to assume its definitive position in the anterior neck. Failure of thyroglossal duct obliteration results in the potential for the cyst to develop. (Right) Axial CT shows a lobulated, low-attenuation, nonenhancing mass embedded within the strap muscles at the level of the hyoid bone, extending into the preepiglottic space without direct connection to the airway.

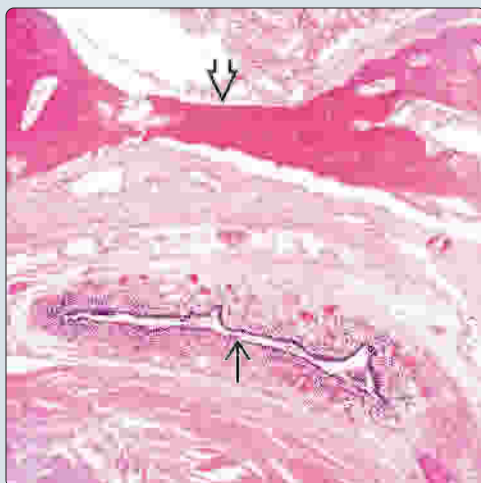


Imaging of Thyroglossal Duct Cyst



Thyroglossal Duct Cyst & Hyoid Bone

(Left) Low magnification shows the presence of an epithelial-lined cyst in relationship to the resected hyoid bone. Note the absence of thyroid follicles in association with the cystic epithelial lining; nevertheless, given the location of the lesion, the findings would support a diagnosis of a thyroglossal duct cyst. (Right) Resection of midline neck mass in the area of hyoid bone shows a cyst with cuboidal to columnar epithelial lining, fibrous wall, and benign thyroid tissue within the cyst wall.



Thyroid Parenchyma in TGDC



TERMINOLOGY

Abbreviations

- Thyroglossal duct cyst (TGDC)

Definitions

- Persistence and cystic dilatation of thyroglossal duct in midline of neck

ETIOLOGY/PATHOGENESIS

Idiopathic

- No known etiology

Thyroid Embryogenesis

- Thyroid follicular epithelium develops from foramen cecum at base of tongue
 - Migration is in midline in caudad direction until situated in normal anatomic position in midline cervical neck
- TGDC develops along path of embryologic development of thyroid gland
- Thyroglossal duct
 - Normally undergoes obliteration by 6 weeks of gestation
 - Failure of thyroglossal duct obliteration results in potential for cyst to develop

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~ 5-7% of population have TGDC
 - Represent ~ 60-70% of congenital neck cysts
 - 2x as common as branchial cleft cysts
- Age
 - Occurs over wide range
 - Majority occur prior to 4th decade of life
- Sex
 - Equal gender distribution

Site

- Majority (~ 75%) occur in midline neck at or just below level of hyoid bone
 - Nearly always connected to hyoid bone
 - ~ 25% are suprahyoid with 2-4% at base of tongue
 - Uncommonly may occur lateral to midline but
 - Lateral localization may occur in setting of significant inflammation and fibrosis or prior surgery
 - Do not occur in lateral portion of neck (i.e., lateral to jugular vein, carotid artery)
 - May be site of recurrent infections
 - Fistulas may develop secondary to infection and open into pharynx or skin

Presentation

- Asymptomatic midline neck mass
 - Typically moves upward on swallowing
 - Inflamed or infected TGDCs may be associated with tenderness and pain
 - Extrinsic airway compression in neonates may be associated with
 - Apnea
 - Cyanosis

- Respiratory compromise

Treatment

- Surgical approaches
 - Sistrunk procedure is treatment of choice, which includes
 - En bloc surgical resection of cyst
 - Middle 1/3 of hyoid bone
 - Suprahyoid tract up to foramen cecum (at base of tongue)

Prognosis

- Adequate surgery results in cure
 - Low, if any, recurrence(s)

IMAGING

Radiographic Findings

- Midline round or elongated cystic lesion
- Expansion &/or destruction of cartilaginous structure of hyoid bone may be seen
- Seldom contains enough thyroid follicular tissue to be seen on scintiscan

CT Findings

- Presence of nodular soft tissue excrescences in midline cystic neck mass
 - May suggest possibility of papillary carcinoma arising in TGDC

MACROSCOPIC

General Features

- Smooth-walled cystic structures
- Cystic content includes clear mucinous fluid
 - Infected cysts contain purulent material

Size

- Usually measure < 2 cm

MICROSCOPIC

Histologic Features

- Epithelial-lined cystic proliferation within (hyoid) bone
- Cyst lining
 - In noninflamed cysts, lined by
 - Respiratory (columnar) epithelium, may include cilia, nondescript cuboidal epithelium or squamous epithelium
 - In presence of inflammation, cyst lining may undergo squamous metaplasia
- Presence of thyroid tissue in cyst wall varies
 - May be dependent on extent of specimen sampling
 - Generally, thyroid tissue found in > 50% of cases
 - Thyroid tissue may be normal, hyperplastic and nodular, or neoplastic
- Fibrosis and chronic inflammatory cell infiltrate seen in cyst wall
- Cholesterol granulomas rarely identified
- Benign and malignant neoplasms may occur in setting of TGDCs including
 - Follicular adenoma
 - Papillary thyroid carcinoma
 - Follicular carcinoma

- Development of carcinoma in TGDC is rare
 - Most common carcinoma to develop in TGDCs is papillary thyroid carcinoma
- **Papillary thyroid carcinoma (PTC) arising in TGDC**
 - Occur more commonly in women than men
 - Occur over wide age range (1st-8th decades of life)
 - Usual type
 - Variant types may include follicular variant, tall cell variant
 - Presence of PTC in setting of TGDC, evaluation of thyroid gland proper is indicated to exclude primary thyroid gland origin
 - Treated similar to TGDCs without associated carcinoma
 - No clear consensus exists regarding optimal management, which may include Sistrunk procedure alone; Sistrunk procedure with total thyroidectomy; Sistrunk procedure with total thyroidectomy and neck dissection
 - Similar (excellent) prognosis to that of thyroid-based papillary carcinoma
 - May recur or metastasize
 - Rarely may be lethal
- Other types of carcinomas in TGDCs are rare and may include
 - Squamous (epidermoid) carcinoma: In all probability arises from cyst lining rather than from thyroid component
 - Undifferentiated (anaplastic) thyroid carcinoma
- C cell-related lesions including medullary carcinoma do not occur in TGDCs
 - Embryologic derivation of C cells differs from follicular epithelial cells
 - C cells develop from ultimobranchial apparatus via neural crest rather than from lingual-based foramen cecum
 - C cells migrate to lateral thyroid lobes
 - C cells do not migrate in midline as do follicular epithelial cells
 - C-cell lesions including medullary carcinoma do not occur in isthmus portion of thyroid gland

ANCILLARY TESTS

Cytology

- Smears from TGDCs are
 - Low in cellularity
 - Inflammatory cells more numerous than epithelial cells
 - Inflammatory cells, especially mature lymphocytes, frequently present
 - Squamous or respiratory epithelium may be identified
- Presence of papillary carcinoma can be diagnosed by fine-needle aspiration
 - Diagnosis based on diagnostic nuclear alterations
 - Nuclear enlargement
 - Variation in nuclear size and shape
 - Optically clear ("Orphan Annie") to dispersed (very fine) appearing nuclear chromatin
 - Nuclear crowding and overlapping
 - Nuclear grooves
 - Intranuclear inclusions

DIFFERENTIAL DIAGNOSIS

Branchial Cleft Cyst

- Generally located in lateral neck not in midline neck
- Lack connection to hyoid bone
- Absence of thyroid follicles

Cervical Thymic Cyst

- Generally not located &/or connected to hyoid bone
- Presence of thymic tissue; absence of thyroid follicles

Metastatic (Cystic) Papillary Thyroid Carcinoma (PTC)

- Histology of metastasis identical to primary TGDC PTC
- Differentiation of primary PTC in TGDC from metastatic papillary carcinoma predicated on
 - Clinical features and radiologic evaluation
 - Transition from benign TGDC lining cells to PTC may be seen and while uncommon supports primary TGDC origin

Other Cysts (Dermoid Cyst, Epidermal Inclusion Cyst, Bronchial Cyst)

- Typically not associated with &/or located at hyoid bone
- Variable epithelial cell lining these cysts may be similar to that seen in TGDC; differentiation predicated on
 - Lack of association with hyoid bone
 - Absence of thyroid follicles
- Dermoid cysts include adnexal structures, which are absent in TGDC
- Epidermal inclusion cysts typically lined by keratinizing squamous epithelium with distinct granular layer containing lamellated keratin, which is absent in TGDC
- Wall of bronchial cysts may include bronchial glands, hyaline cartilage &/or smooth muscle, which are absent in TGDC

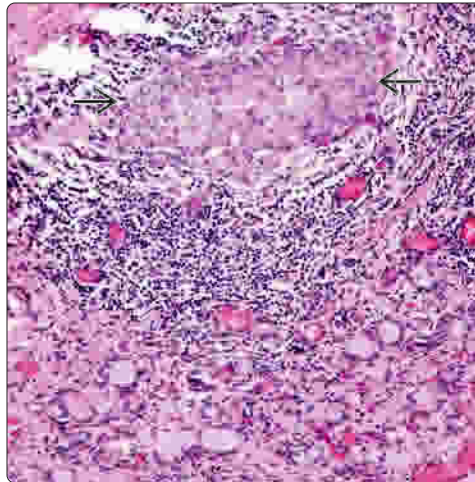
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Thyroid Follicular Epithelium in TGDC

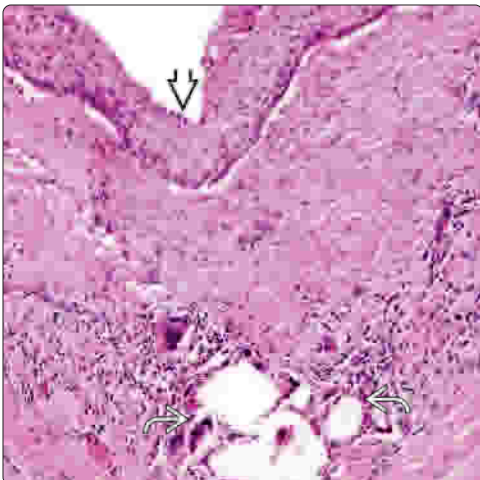


Squamous Metaplasia in TGDC



(Left) Colloid-filled thyroid follicular epithelium is shown within the cyst wall. The presence of thyroid tissue in cyst wall varies and may be dependent on the extent of specimen sampling. Of note, the absence of thyroid tissue does not exclude the diagnosis. **(Right)** The thyroid tissue in thyroglossal duct cysts is mostly normal-appearing but may include secondary retrogressive changes including chronic inflammatory cell infiltrates and squamous metaplasia.

Reactive Changes of Cyst Lining

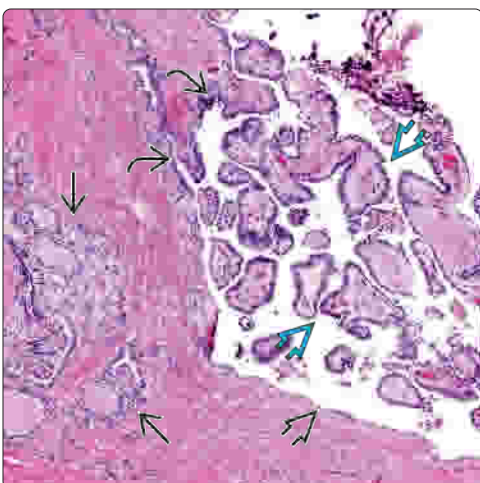


Papillary Thyroid Carcinoma in TGDC

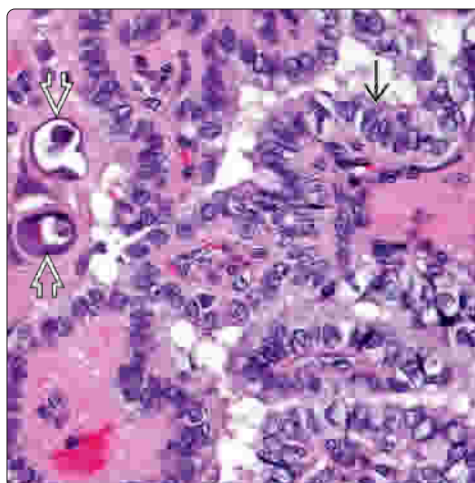


(Left) TGDCs may be the site of recurrent infections resulting in squamous metaplasia of the cyst lining. The cyst wall is fibrotic with chronic inflammation and cholesterol granuloma formation but absent thyroid tissue. Identifying thyroid tissue may require extensive sampling. **(Right)** Axial CT reveals a complex cystic and solid midline mass at hyoid bone level. Enhancing nodule with calcification is highly suggestive of papillary carcinoma arising in TGDC.

Papillary Architecture and Invasion



Diagnostic Nuclei and Psammoma Bodies



(Left) Papillary thyroid carcinoma arising in TGDC shows transition from nonneoplastic cyst lining to neoplastic proliferation of the cyst epithelial lining as well as intracystic papillary growth. The carcinoma is invasive into the cyst wall. **(Right)** Diagnostic nuclear features of papillary carcinoma include nuclear enlargement with variation in size and shape, optically clear to dispersed nuclear chromatin, crowding and overlapping, and nuclear grooves. In addition, psammoma bodies are present.

KEY FACTS

TERMINOLOGY

- Presence of otherwise normal thyroid parenchyma in any location other than its normal anatomic position
- Ectopic thyroid tissue may represent failure of descent from foramen cecum (median anlage)
- Thyroid follicular epithelium develops from foramen cecum located at base of tongue
 - Migration is in midline in caudad direction until situated in normal anatomic position in midline cervical neck

CLINICAL ISSUES

- Ectopic thyroid tissue may be seen in any location from tongue (foramen cecum at base of tongue) to suprasternal notch (site of normal gland)
- Excluding thyroglossal duct cyst, presence of ectopic thyroid tissue rare and almost exclusively seen in suprahyoid locations usually located in or close to midline
- Most common thyroid ectopia is at base of tongue (referred to as lingual thyroid)

- Rarely, dual thyroid ectopia occurs, including separate ectopic sites occurring in same patient
- In general, ectopic thyroid tissue is benign
 - Malignant neoplasms may arise in thyroid ectopia, including papillary thyroid carcinoma and follicular carcinoma

MICROSCOPIC

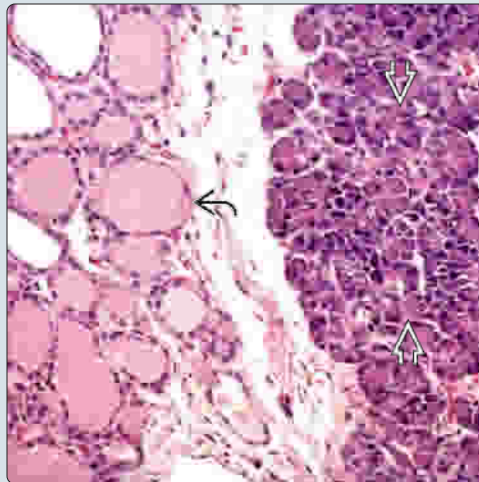
- Normal-appearing thyroid tissue (i.e., colloid-filled follicles)
- Neuroendocrine C cells not identified
- Normal thyroid tissue can be found within skeletal muscle &/or fat of cervical neck

ANCILLARY TESTS

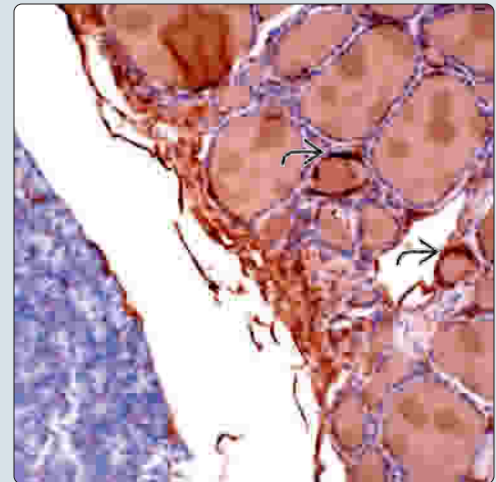
- Positive for thyroglobulin, TTF-1 (nuclear), pax-8 (nuclear), CD56
- Few reports evaluating molecular alterations in thyroid ectopia were without molecular alterations associated with malignant follicular tumors (e.g., *BRAFV600E*, *RAS*)

Intrapancreatic Benign Thyroid Tissue

(Left) Intrapancreatic ectopic thyroid tissue is from a patient with pancreatic resection for pancreatic adenocarcinoma. The thyroid tissue was an incidental finding lacking nuclear features for papillary thyroid carcinoma. Subsequent work-up revealed a normally situated thyroid gland without identifiable lesions (e.g., follicular carcinoma). (Right) The intrapancreatic thyroid tissue is immunoreactive for thyroglobulin, confirming the ectopia as definitively being of thyroid follicular epithelial origin.

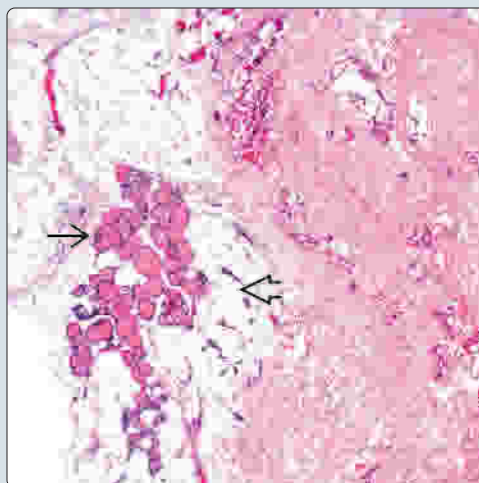


Intrapancreatic Benign Thyroid Tissue

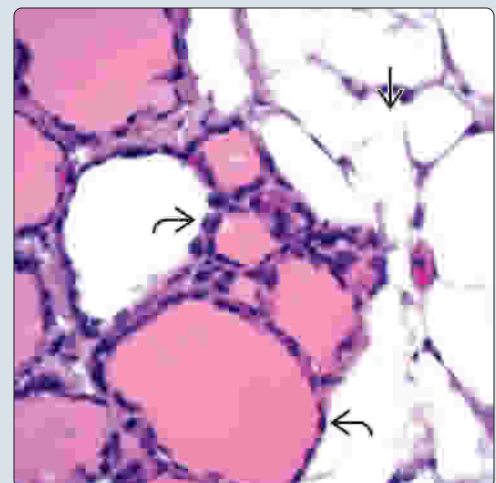


Thyroid Tissue in Fat

(Left) Thyroid follicular epithelium in mature adipose tissue is located near to but completely outside of the thyroid gland proper. Note the absence of associated desmoplasia. (Right) Thyroid follicular epithelium in perithyroidal fat is within histologic normal limits lacking nuclear features diagnostic for papillary thyroid carcinoma. This is a developmental abnormality and should not be mistaken for the presence of a malignant neoplasm.



Thyroid Tissue in Fat



TERMINOLOGY

Synonyms

- Aberrant thyroid rests; thyroid heterotopia; thyroid choristoma

Definitions

- Presence of otherwise normal thyroid parenchyma in any location other than its normal anatomic position

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Ectopic thyroid tissue may represent failure of descent from foramen cecum (median anlage)
- Less likely, ectopia occurs via differentiation of thyroid tissue in abnormal locations
- Complete or partial agenesis of thyroid gland is extremely rare
- Rarely, familial thyroid ectopia may occur

Thyroid Embryogenesis

- Thyroid follicular epithelium develops from foramen cecum located at base of tongue
 - Migration is in midline in caudad direction until situated in normal anatomic position in midline cervical neck
 - Failure to migrate may result in ectopia anywhere along midline descent from foramen cecum to cervical neck
- Thyroid neuroendocrine cells (C cells) develop from neural crest
 - Migrate to ultimobranchial apparatus located in 3rd-4th branchial arches
 - C cells migrate only to lateral lobes of thyroid gland
 - C cells do not migrate in midline fashion
 - C cells not found in isthmus portion of thyroid gland

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare
- Age
 - Any age
- Sex
 - Equal gender distribution

Site

- Ectopic thyroid tissue seen in any location from tongue (foramen cecum at base of tongue) to suprasternal notch (site of normal gland)
- Excluding thyroglossal duct cyst, presence of ectopic thyroid tissue rare
 - Almost exclusively seen in suprahyoid locations usually located in or close to midline
 - Most common thyroid ectopia is at base of tongue (referred to as lingual thyroid)
 - Other sites include (from cranial to caudal direction)
 - Sella turcica, submandibular region; larynx, trachea, mediastinum (superior > posterior), aortic arch, pericardium, heart, esophagus
 - More distant sites of ectopic thyroid tissue include

- Hepatobiliary (liver, porta hepatis, gallbladder, common bile duct), pancreas, adrenal gland, retroperitoneum, vagina, and inguinal region
- Ovarian thyroid tissue (referred to as struma ovarii)
- Rarely, dual thyroid ectopia occurs, including separate ectopic sites occurring in same patient
- Orthotopic thyroid gland usually present but may be absent
 - Ectopic thyroid tissue may represent only thyroid tissue present

Presentation

- Excluding thyroglossal duct cyst and lingual thyroid, majority of thyroid ectopia are asymptomatic
- Depending on location, presentation may include
 - Local obstruction, presence of mass, stridor, hemorrhage, heart murmur, &/or voluminous cardiac mass resembling cardiac tumor

Laboratory Tests

- Ectopic thyroid may function abnormally, including laboratory evidence of hypothyroidism and hyperthyroidism

Prognosis

- In general, ectopic thyroid tissue is benign
 - Different types of malignant neoplasms may arise in thyroid ectopia, including papillary thyroid carcinoma (PTC) and follicular carcinoma

MICROSCOPIC

Histologic Features

- Normal-appearing thyroid tissue (i.e., colloid-filled follicles)
- Neuroendocrine C cells not identified
- Cytomorphologic features of PTC absent
- **Thyroid inclusions in lymph nodes**
 - Controversial issue whether benign intranodal thyroid inclusions exist or whether all nodal-based thyroid tissue represents metastatic PTC
 - Benign thyroid inclusions in lymph nodes may occur but require strict criteria including
 - Lymph node located in midline or medial to jugular vein
 - Thyroid tissue located in nodal capsule and not found in several lymph nodes &/or replaces nodal parenchymal tissue
 - Inclusions are few in number (e.g., 2-3 follicles) and cytologically bland without histologic features of PTC
 - Primary thyroid carcinoma is not present
- **Thyroid tissue in perithyroidal soft tissues**
 - Normal thyroid tissue can be found within skeletal muscle &/or fat of cervical neck
 - Reflects developmental abnormality and should not be mistaken for malignancy
 - Thyroid in skeletal muscle often seen in relation to isthmus portion of gland
 - Mature adipose tissue can be found in wide variety of intrathyroidal lesions

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** Thyroglobulin, TTF-1 (nuclear), pax-8 (nuclear), CD56
- Cytokeratins positive
- Calcitonin and neuroendocrine markers negative

Genetic Testing

- Few reports evaluating molecular alterations in thyroid ectopia were without molecular alterations associated with malignant follicular tumors (e.g., *BRAFV600E*, *RAS*)

DIFFERENTIAL DIAGNOSIS

Metastatic Papillary Thyroid Carcinoma

- Demonstrate diagnostic nuclear features
- Any thyroid tissue found in lymph nodes lateral to great vessels (jugular vein, carotid artery) represents metastatic PTC
 - Should be considered metastatic even in absence of unequivocal diagnostic nuclear features
- Nodal metastasis may be identified incidentally in neck dissection for other reasons, including staging neck dissection for other head and neck carcinomas (e.g., mucosal-based squamous cell carcinoma)
- In presence of PTC in thyroid gland proper
 - Presence of thyroid tissue in ectopic sites, especially lymph nodes, in all probability represents metastatic disease

Mediastinal Thyroid (Substernal Goiter)

- Represents goitrous thyroid extending from thyroid gland proper into mediastinum (substernal or retrosternal)
- As multinodular goiter enlarges, it has tendency to move inferiorly due to fascial planes favoring this migration
- Most mediastinal goiters are benign (adenomatoid nodules)
 - Thyroid malignancies (papillary carcinoma, follicular carcinoma, anaplastic carcinoma) can be seen in mediastinal thyroid tissue
- Mediastinal goiters generally do not respond to thyroid suppression and require surgical removal
 - Due to risk of sudden enlargement with possibility of airway compression or obstruction, intrathoracic goiters should be surgically removed

Parasitic Nodule (Lateral Aberrant Thyroid)

- Represents part of goitrous thyroid in which
 - Peripherally located nodule(s) anatomically separated from main gland in soft tissues of neck
 - Aberrant tissue may be connected to thyroid by thin fibrous strand that may or may not be appreciated by surgeon
 - May erroneously be considered malignant given localization away from thyroid gland
 - Pathologic findings may include adenomatoid nodule(s) &/or chronic lymphocytic thyroiditis (CLT)
 - Care should be taken not to interpret thyroid tissue in CLT as within lymph node
 - May lead to erroneous diagnosis of metastatic PTC
 - There is no subcapsular sinus or other feature of lymph nodes

- Stipulations for diagnosis include
 - Thyroid tissue not in lymph node parenchyma
 - Aberrant thyroid tissue without nuclear features of PTC

Mechanical Implantation

- Thyroid tissue (normal or hyperplastic) unattached to thyroid gland in neck
 - May be result of prior surgery or accidental trauma
 - Presence of fibrotic reaction &/or suture material in association with thyroid tissue

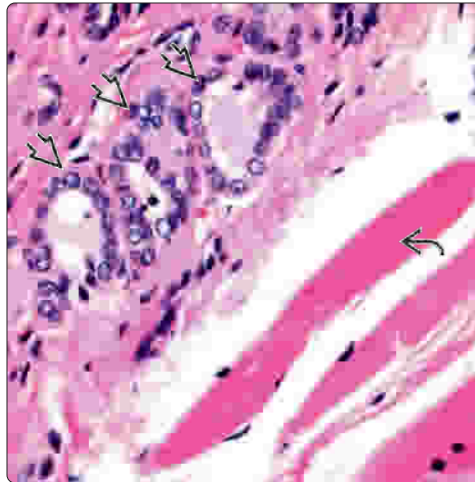
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Thyroid Tissue in Skeletal Muscle

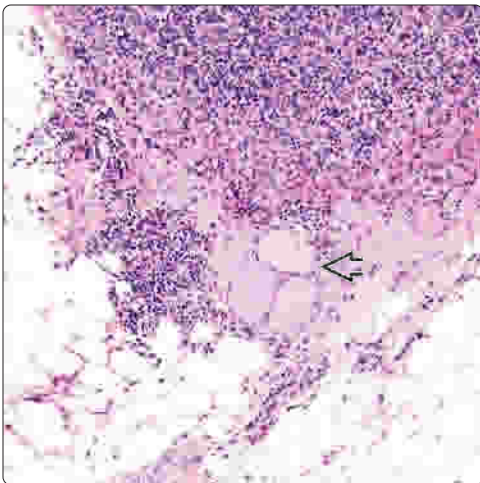


Thyroid Tissue in Skeletal Muscle

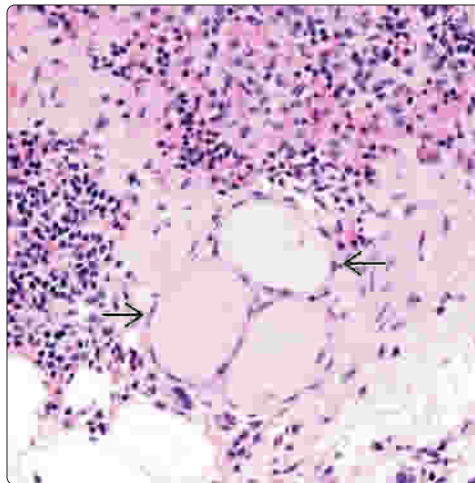




(Left) Thyroid follicular epithelium  in skeletal muscle  lying outside the gland proper is a normal developmental finding typically seen in association with the isthmic portion of the thyroid gland. Note the absence of associated desmoplasia. (Right) Thyroid follicular epithelium  in skeletal muscle  is within normal limits, lacking nuclear features of papillary thyroid carcinoma. Furthermore, there was no evidence of a follicular carcinoma in the gland proper that might have shown extrathyroidal extension.

Lymph Node With Thyroid Inclusions



Lymph Node With Thyroid Inclusions

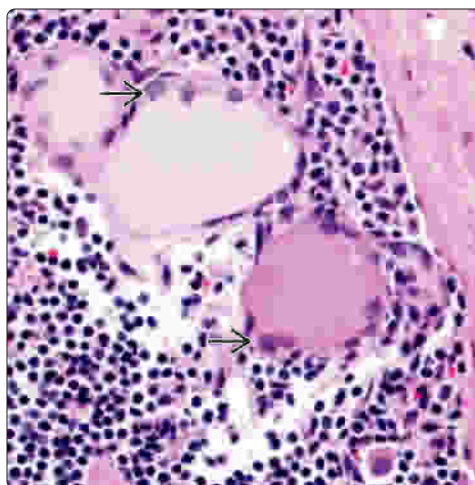





(Left) Midline lymph node shows the presence of limited (3) colloid-filled thyroid follicles  identified in the capsule of the lymph node and not within the parenchyma. (Right) The nuclei  associated with the follicles are bland, lacking diagnostic features for papillary thyroid carcinoma. Given the midline location of the lymph node, presence of limited follicles within the capsule and not parenchyma, and absence of diagnostic nuclear features, the findings represent benign thyroid inclusions.

Metastatic Papillary Thyroid Carcinoma



Metastatic Papillary Thyroid Carcinoma



(Left) In contrast to the 2 prior images, in this example, 3 colloid-filled thyroid follicles  are located within the parenchyma and not in the capsule  of the lymph node. (Right) The nuclei  are not diagnostic for papillary thyroid carcinoma (PTC). Nevertheless, metastatic PTC is diagnosed based on the parenchymal involvement (rather than capsular localization), despite the limited volume of the lesion and absence of diagnostic nuclear features. A primary ipsilateral PTC was present (not shown).

KEY FACTS

TERMINOLOGY

- Small remnant of ultimobranchial apparatus, associated with development of thyroid C cells

CLINICAL ISSUES

- Posteromedial and lateral area of bilateral middle to upper 1/3 of thyroid lobes

MACROSCOPIC

- < 0.1 cm: 50-1,000 µm in greatest dimension

MICROSCOPIC

- 4 types are recognized
- **Type 1:** Small round or oval groups or clusters of elongated cells and scant cytoplasm (floret-like or main cells)
 - Small epithelial cells, ovoid to polygonal; rarely spindled
 - Often there are C cells within proliferation
 - Distinct eosinophilic basement membrane surrounds groups

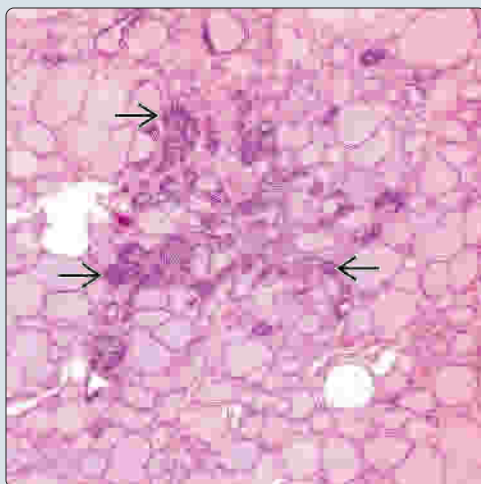
- Nuclei are ovoid, with evenly distributed, finely granular chromatin
- Frequent longitudinal nuclear groove
- **Type 2:** Large polygonal cells with abundant cytoplasm and distinct cell boundaries
 - No keratinization or intercellular bridges
- **Type 3:** Cystic structure lined by polygonal to flattened cells
 - Lesions may be partially cystic (up to 55%)
- **Type 4:** Structures lined by main cells and follicular epithelium

ANCILLARY TESTS

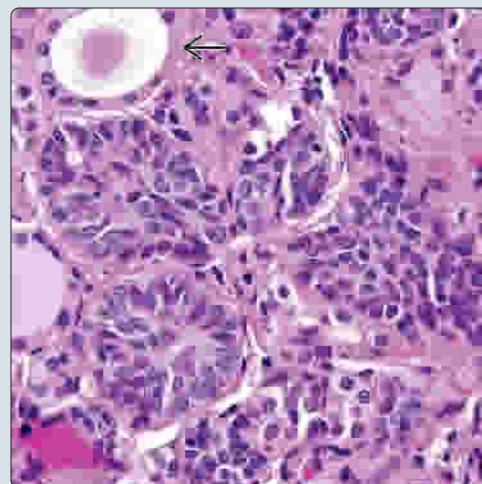
- Strongly **positive:** p63 (may be compartmentalized), carcinoembryonic antigen (pCEA), high and low molecular weight keratins, neurotensin, somatostatin, galactin 3; sometimes HBME-1
- **Negative:** Thyroglobulin, TTF-1

(Left) At low power, the lobulated small nests [B] are easily identified in the background thyroid follicular epithelium. However, squamous metaplasia can appear identical from low power. (Right) The cells are epithelial and oval, with oval nuclei. The nuclear chromatin is delicate and even, with a longitudinal nuclear groove. Adjacent follicular epithelium shows slightly oncocytic change [B].

Type 1: Solid Cell Nests at Low Power



Type 2: Oval, Bland Nuclei in Solid Cell Nest

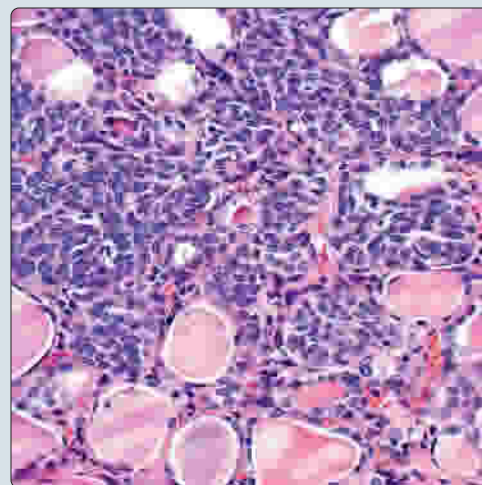


(Left) Cystic change can be seen in solid cell nest (SCN). The cells are epithelial and oval, with oval nuclei. The nuclear chromatin is delicate and even, with a longitudinal nuclear groove. Intercellular bridges are absent. (Right) In many SCNs, the epithelial cells show a compact arrangement, surrounded by a basement membrane. The cells are epithelial and oval, with oval nuclei. The nuclear chromatin is delicate and even, with a longitudinal nuclear groove. Intercellular bridges are absent.

Type 3: Cystic Change in Solid Cell Nest



Type 1: Cells With Longitudinal Groove



TERMINOLOGY

Abbreviations

- Solid cell nests (SCNs)
- Ultimobranchial body (UBB)

Definitions

- Small remnant of ultimobranchial apparatus, associated with development of thyroid C cells

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Branchial pouch remnants
- Ultimobranchial body vestiges (endoderm)
 - High density of C cells intermingled with SCNs

CLINICAL ISSUES

Epidemiology

- Incidence
 - Present in all thyroid glands if sought
 - Incidental finding in ~ 25% of thyroid specimens

Site

- Posteromedial and lateral area of bilateral middle to upper 1/3 of thyroid lobes
- Never in isthmus

Presentation

- Incidental, discovered by extensive sampling
- Possibly increased frequency in patients with
 - Chronic lymphocytic thyroiditis (Hashimoto)
 - Medullary thyroid carcinoma and C-cell hyperplasia

MACROSCOPIC

Sections to Be Submitted

- Middle to upper 1/3 of thyroid lobes, outer to lateral-posterior area

Size

- < 0.1 cm: 50 to 1,000 µm in greatest dimension

MICROSCOPIC

Histologic Features

- 4 types are recognized
- **Type 1:** Small round or oval groups or clusters of elongated cells and scant cytoplasm (floret-like or main cells)
 - Small epithelial cells, ovoid to polygonal; rarely spindled
 - Often there are C cells within proliferation
 - C cells have granular-bluish cytoplasm
 - Distinct eosinophilic basement membrane surrounds groups
 - Nuclei are ovoid, with evenly distributed, finely granular chromatin
 - Frequent longitudinal nuclear groove
 - Amphophilic to occasionally clear cytoplasm
- **Type 2:** Large polygonal cells with abundant cytoplasm and distinct cell boundaries
 - No keratinization or intercellular bridges
- **Type 3:** Cystic structure lined by polygonal to flattened cells

- Lesions may be partially cystic (up to 55%)
- **Type 4:** Structures lined by main cells and follicular epithelium
 - Interfollicular distribution of well-demarcated nests
 - Follicular epithelium frequently interspersed or trapped
- Degeneration may result in mucicarminophilic mucoid material or concretions
 - Goblet cells may be seen within epithelial nests
 - Ciliated columnar cells are uncommon

ANCILLARY TESTS

Immunohistochemistry

- Strongly **positive:** p63 (may be compartmentalized), carcinoembryonic antigen (pCEA), high and low molecular weight keratins, neurotensin, somatostatin, galactin 3; sometimes HBME-1
- C cells highlighted with **positive:** Chromogranin-A, synaptophysin, calcitonin, calcitonin gene-related peptide, neuron-specific enolase
- **Negative:** Thyroglobulin, TTF-1

Genetic Testing

- **Negative:** *BRAF*, *GRIM-19*

DIFFERENTIAL DIAGNOSIS

Squamous Metaplasia

- Multifocal throughout gland, showing intercellular bridges, keratinization
- Usually associated with other disorders (chronic lymphocytic thyroiditis, carcinomas)

Papillary Thyroid Carcinoma (Microscopic)

- Microscopic, solid or cystic
- Infiltrative pattern with heavy sclerosis/desmoplasia
- Enlarged, overlapping cells, with grooves, contour irregularities, intranuclear cytoplasmic inclusions
- **Positive:** Thyroglobulin, TTF-1

Inclusions

- Normal thymic tissue (Hassall corpuscles; lymphoid tissue), parathyroid gland (cleared cytoplasm, well-defined cell borders), and salivary gland tissue
- Histologically distinct and different from SCNs

Metastatic Squamous Cell Carcinoma

- Lymphatic location, marked pleomorphism, mitotic figures, keratinization, and intercellular bridges

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KEY FACTS

TERMINOLOGY

- Thyroid enlargement due to hereditary defect in thyroid hormone synthesis

ETIOLOGY/PATHOGENESIS

- Deficiency in thyroperoxidase (TPO) activity is most frequent cause of dyshormonogenetic goiter

CLINICAL ISSUES

- Usually autosomal recessive, enzyme defect in one of the biochemical steps of thyroid hormone synthesis
- Congenital hypothyroidism: 1 in 3,000-4,000 births
 - ~ 15% due to dyshormonogenetic goiter
- Average age at presentation: 16 years
- Absent or severely decreased thyroid hormone synthesis
 - Low to absent T4 and T3, with high TSH
- Treatment of hypothyroidism is primary goal, with replacement hormone and surgery for symptomatic goiter

MACROSCOPIC

- Entire thyroid gland affected
- Thyroid is enlarged, asymmetric, and nodular, resembling adenomatoid nodules
 - But colloid is not seen on cut surface

MICROSCOPIC

- All thyroid tissue is abnormal
- Nodules vary considerably but hypercellular with scant/absent colloid
- Pleomorphism highlighted or accentuated in cells between nodules
 - In fibrous septa or internodular parenchyma

TOP DIFFERENTIAL DIAGNOSES

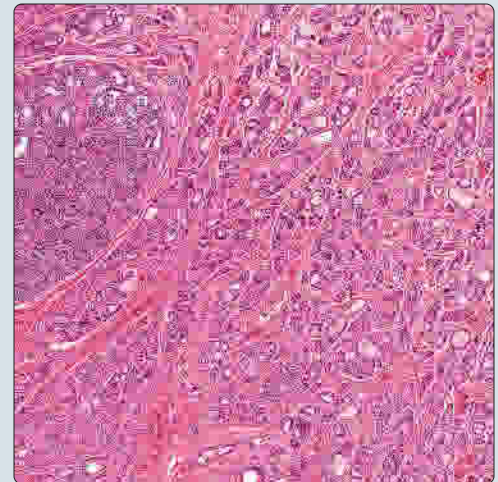
- Adenomatoid nodules, diffuse hyperplasia (Graves disease), radiation thyroiditis, follicular carcinoma, iatrogenic goiter

(Left) The thyroid gland is asymmetric and nodular, with the nodules resembling adenomatoid nodules. There is colloid present, although it is not prominent. The nodules are cellular. **(Right)** There is a vague nodularity to this thyroid section. Note the variable colloid appearance and overall increased cellularity and fibrosis.

Multiple Nodules With Diminished Colloid

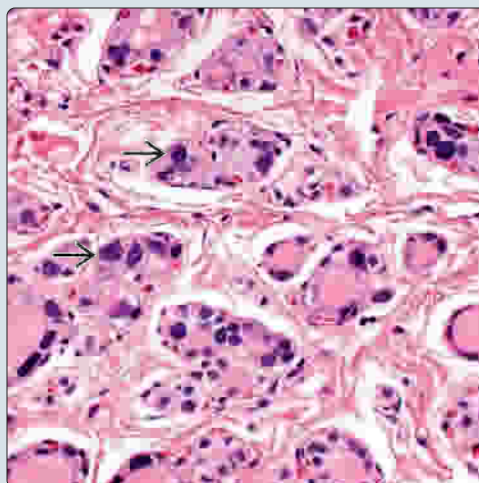


Hyperplasia With Decreased Colloid

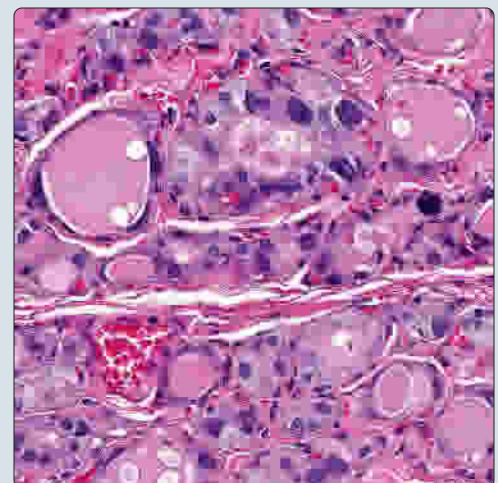


(Left) Within the septal regions of the gland, there are a number of isolated, highly atypical cells. Note the variability in the colloid in this high-power field. There is also a background of fibrosis. **(Right)** Isolated, profoundly pleomorphic nuclei are seen within the tissue between the nodules of a dyshormonogenetic goiter. There is no atypia within the nodules, a characteristic feature of this disorder.

Marked Nuclear Pleomorphism in Septa



Nuclear Pleomorphism in Septa



TERMINOLOGY

Definitions

- Thyroid enlargement due to hereditary defect in thyroid hormone synthesis

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Genetic defect in one of the biochemical steps of thyroid hormone synthesis
 - Usually autosomal recessive
 - Several major enzyme defects are known
 - Loss of any of genes involved in thyroglobulin synthesis, iodine transport, iodide oxidation and organification, coupling of MIT and DIT, proteolytic breakdown of thyroglobulin, and iodide recycling
 - Deficiency in thyroperoxidase (TPO) activity is most frequent cause of dyshormonogenetic goiter

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very rare cause of permanent congenital hypothyroidism
 - 2nd most frequent cause of permanent congenital hypothyroidism
 - Congenital hypothyroidism (thyroid dysgenesis): 1 in 3,000-4,000 births
 - About 15% due to dyshormonogenetic goiter
 - Prevalence of dyshormonogenetic goiter: 1 in 30,000-50,000 population
- Age
 - Mean: 16 years; range: Neonates to adults
 - Majority manifest before age 25 years
- Sex
 - Female slightly > male

Site

- Entire thyroid gland affected
 - Whenever whole thyroid is affected, must consider genetic or autoimmune etiologies

Presentation

- Absent or severely decreased thyroid hormone synthesis
 - Results in increased, continuous secretion of TSH due to functional hypothyroidism
 - Insufficient hormone production for feedback loop
 - Yields thyroid hyperplasia without thyroid function improvement
- Only patients with most severe impairment in thyroid hormone production present in infancy with cretinism
- Most patients (2/3) have known hypothyroidism prior to recognition of goiter
 - Thyroid enlargement (goiter) tends to develop later in life
- Family history of hypothyroidism is elicited in only 20% of patients
- Pendred syndrome very rare (*SLC26A4* at 7q31)
 - Association of dyshormonogenetic goiter (impaired iodide organification) with familial deaf-mutism due to sensorineural deafness

- Biallelic mutations in *SLC26A4* gene

Laboratory Tests

- Low to absent T4 and T3; high TSH

Natural History

- If severe or complete, cretinism at birth
- Death if there is no replacement therapy

Treatment

- Treatment of hypothyroidism is primary goal
 - Replacement hormone manages hypothyroidism
 - Levothyroxine (Synthroid)
- Total thyroidectomy for symptomatic goiter

Prognosis

- Excellent outcome with thyroid hormone replacement therapy
- No increased risk of thyroid carcinoma
 - If carcinoma does develop, no difference in long-term prognosis

MACROSCOPIC

General Features

- Thyroid is enlarged, asymmetric, and nodular
- Enlargement varies from mild to marked
- Nodules resemble adenomatoid nodules
 - But colloid is not seen on cut surface
 - Nodules tend to be more opaque instead of translucent (like adenomatoid nodules)

Sections to Be Submitted

- Junction of nodules to intervening parenchyma (fibrovascular septa)
- Must sample any encapsulated lesions thoroughly

Size

- Up to 600 g, but usually 50-250 g

MICROSCOPIC

Histologic Features

- All thyroid tissue is abnormal
 - Distinctly different from relatively normal thyroid seen between adenomatoid nodules
- Nodules vary considerably
 - Due to different enzyme defects and duration of disease (age of patient) at time of diagnosis
 - Hypercellular nodules, usually solid or microfollicular
 - Papillary, trabecular, or insular patterns may be observed
- Colloid is usually scant to absent
 - When present, it has different color, quality, and quantity than normal colloid
 - Has washed-out, thin or watery appearance
 - Tends to be more easily identified within nodules
- Fibrosis is often a prominent finding
 - Sometimes so extensive it distorts architecture, suggesting invasion
- Cytologic atypia is nearly always present
 - Pleomorphism highlighted or accentuated in cells **between** nodules
 - In fibrous septa or internodular parenchyma

Defects Associated With Dyshormonogenetic Goiter

Steps in Thyroid Hormone Synthesis	Related Gene
Thyroglobulin synthesis	Thyroglobulin (<i>TG</i>)
Iodine transport into follicular cell	Sodium-iodide symporter (<i>SIS</i>)
Iodine transport into lumen	Pendrin (<i>PDS</i>)
Oxidation of iodine	Thyroperoxidase (<i>TPO</i>)
	Dual oxidase genes (<i>DUOX1</i> and <i>DUOX2</i>); a.k.a. thyroid oxidase genes (<i>THOX1</i> and <i>THOX2</i>)
Organification of thyroglobulin	Thyroperoxidase (<i>TPO</i>)
Coupling of MIT and DIT	Thyroperoxidase (<i>TPO</i>)
Proteolytic breakdown of TG	Various lysosomal endopeptidases and exopeptidases
Dehalogenation of MIT and DIT	Dehalogenase 1 (<i>DEHAL1</i>)

DIT = di-iodotyrosine; MIT = mono-iodotyrosine.

- These regions tend to be solid or microfollicular
- Enlarged, hyperchromatic nuclei
- May have contour irregularities and grooves
- o Can be quite striking, similar to radiation thyroiditis

ANCILLARY TESTS

Cytology

- Cannot exclude a follicular neoplasm, but may exclude a papillary carcinoma
- Aspirates are remarkably cellular, often with prominent nuclear atypia
- Little or no colloid

Metabolic Work-Up

- Evaluation of thyroid function and pituitary-thyroid axis

DIFFERENTIAL DIAGNOSIS

Adenomatoid Nodules

- Usually in middle-aged adults with asymmetric thyroid enlargement
- Hyperplasia is only present within nodules, showing easily identified colloid
- Secondary degenerative changes (cyst formation, hemosiderin-laden macrophages, hemorrhage, calcification, fibrosis) more common
- Lacks internodular nuclear atypia

Diffuse Hyperplasia (Graves Disease)

- Clinical hyperthyroidism with autoantibodies detected in serum
- Entire thyroid affected
- Papillary and follicular structures predominate with variably present colloid
- Lacks pleomorphism or atypia
- Lymphoid aggregates (germinal centers) are common finding

Radiation Thyroiditis

- Clinical history of radiation and age of patient at presentation helps
- Frequently has cellular nodules with overall increased fibrosis

- Cytologic atypia is **random** throughout gland, not accentuated in internodular zones

Follicular Carcinoma

- Encapsulated tumor
 - o Capsule is usually quite thick and well formed
 - o Smooth muscle-walled vessels within fibrosis help define capsule
 - o Irregular perinodular fibrosis in dyshormonogenetic goiter can simulate capsular invasion
- Shows definitive capsular &/or vascular invasion
- Cellular atypia is not a diagnostic criterion

Iatrogenic Goiter

- Due to antithyroidal drugs
- May have nodules with limited colloid
- Can be indistinguishable on histologic basis alone

DIAGNOSTIC CHECKLIST

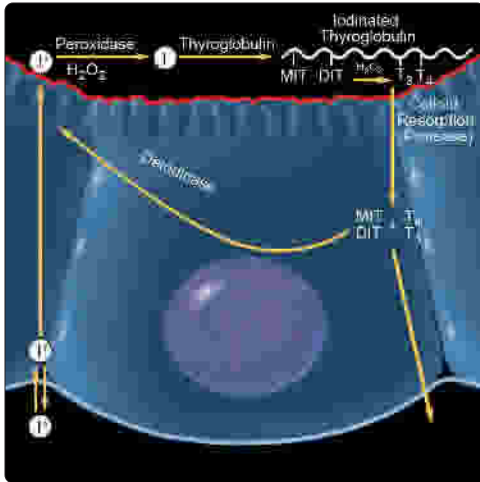
Pathologic Interpretation Pearls

- All of thyroid gland is abnormal
- Bizarre, pleomorphic nuclei in internodular parenchyma
- Limited or thin colloid

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Enzymes in Thyroid Hormone Productions

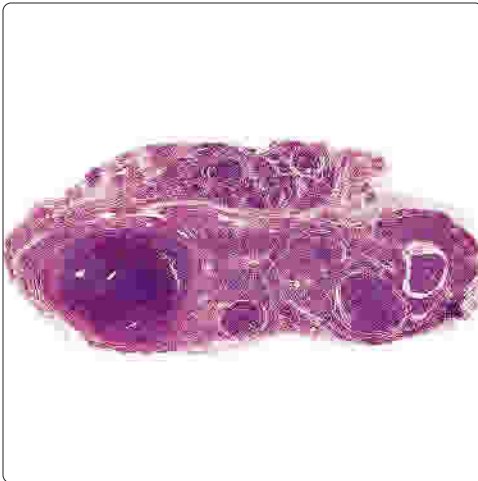


Multiple Nodules With Variable Colloid

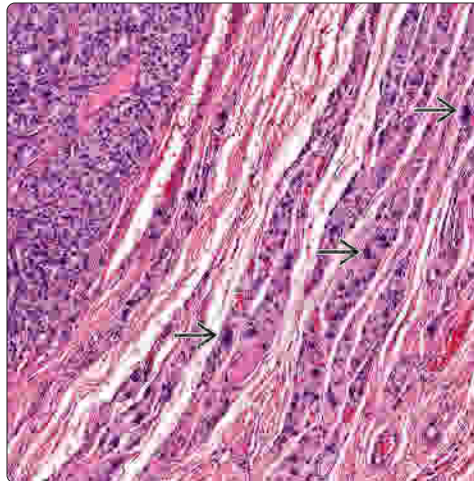


(Left) This graphic shows normal thyroid hormone production pathways. Several major enzyme defects are known, including loss of any of the genes involved in thyroglobulin synthesis, coupling of MIT and DIT, and iodide recycling. (Right) This gross photograph demonstrates a remarkable number of nodules with associated fibrosis; however, it is easy to see that the nodules seem to be quite opaque rather than translucent, a finding seen as a result of changes in colloid quality.

Overall Increased Cellularity

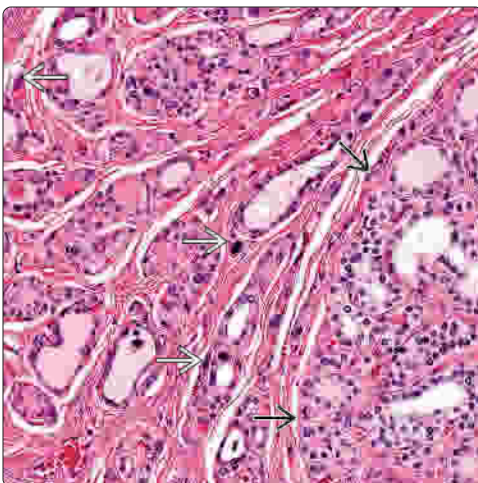


Diminished Colloid With Nodules

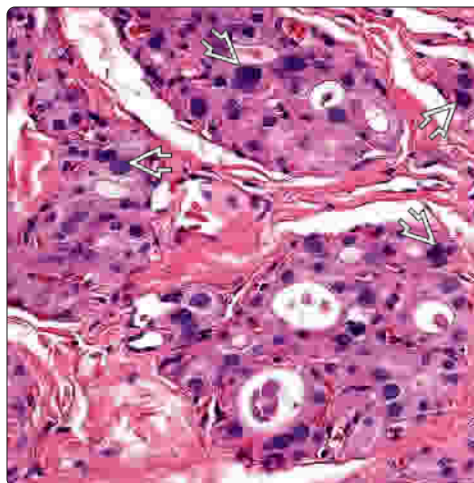


(Left) This low power demonstrates a number of variably sized nodules, along with the remaining thyroid parenchyma showing increased cellularity. (Right) Nodules are cellular, usually without colloid. The intervening septations show increased fibrosis and a number of isolated, remarkably atypical and hyperchromatic nuclei. The atypia is not usually seen within the nodules, only in the septal tissues.

Fibrosis Associated With Nodules



Atypical Follicular Cells, Not Stromal Cells



(Left) The nodule has colloid, although it is thin. There is heavy fibrosis surrounding the nodule, with isolated atypical follicular epithelial cells. (Right) On high power, it is important to note the atypia is within the epithelial cells, not in the stromal cells (the latter seen in radiation thyroiditis). The atypical nuclei are not seen throughout the sample but only in isolation or small clusters.

KEY FACTS

TERMINOLOGY

- Presence of inflammatory cell infiltrate dominated by polymorphonuclear leucocytes within thyroid gland caused by identifiable microorganism

ETIOLOGY/PATHOGENESIS

- Most common causative bacteria include *Streptococcus haemolyticus*, *Staphylococcus aureus*
- Mycobacterial infections are rare, even in patients with miliary tuberculosis
- Fungal infection primarily reported to be *Aspergillus* species
 - Virtually all affected patients are immunocompromised

CLINICAL ISSUES

- Tends to develop in immunocompromised, immunosuppressed, or malnourished patients
- May be part of systemic involvement or associated with localized infection

- Treatment predicated on diagnosis and identification of causative microbe
- Prognosis excellent for bacterial-related acute thyroiditis

MICROSCOPIC

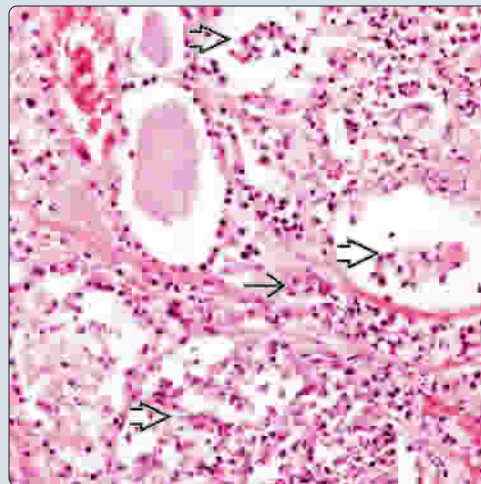
- **Acute thyroiditis**
 - Focal to diffuse neutrophilic infiltrate with destruction of follicular epithelial cells
 - Areas of abscess formation characterized by dense pool of leukocytes can be seen
 - Causative microorganism may or may not be identifiable by light microscopy
- **Granulomatous inflammation**
 - Caseating granulomas with central necrosis surrounded by histiocytic cells &/or multinucleated giant cells
 - Causative microorganism may or may not be identifiable by light microscopy

ANCILLARY TESTS

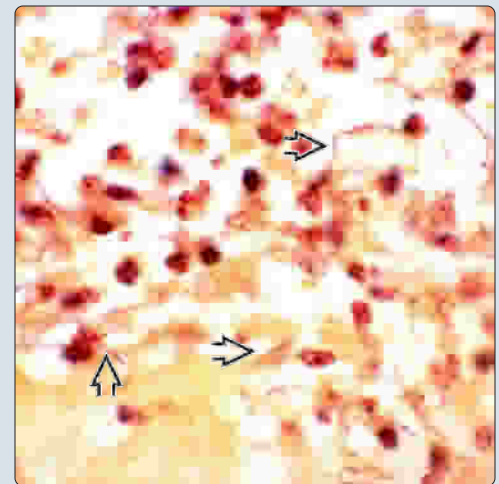
- IHC and ISH may assist in identification of microorganism

Acute Bacterial Thyroiditis

(Left) Acute suppurative thyroiditis shows marked inflammation dominated by polymorphonuclear leukocytes colonizing thyroid follicles [E], as well as located within the intervening stroma [E]. Microorganisms that may be associated with acute thyroiditis include bacteria and fungi. Histochemical stains are indicated. (Right) *Nocardia*, an aerobic, branching, actinomycete, filamentous, gram-positive organism [E], can infect the thyroid, causing suppurative lesions characterized by a neutrophilic cell infiltrate.



Nocardia Thyroiditis

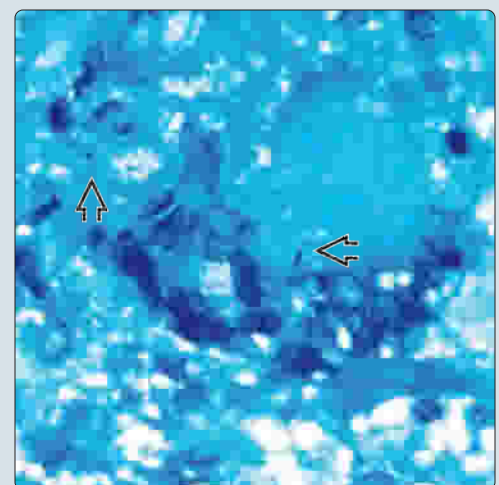


Granulomatous Thyroiditis

(Left) Intrathyroidal [E], well-formed, caseating, granulomatous inflammation with central necrosis [E], palisading histiocytes [E], and multinucleated giant cells [E] is shown. The primary diagnostic consideration would be mycobacterial involvement of the thyroid gland. Histochemical stains are indicated. (Right) Under oil immersion, 2 acid-fast bacillus organisms [E], characterized by a beaded appearance and red color, are seen in multinucleated giant cells and can be difficult to find, even with special stains.



Mycobacterial Tuberculosis



TERMINOLOGY

Synonyms

- Acute suppurative thyroiditis

Definitions

- Presence of inflammatory cell infiltrate dominated by polymorphonuclear leucocytes within thyroid gland caused by identifiable microorganism

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Bacteria, mycobacteria, fungi, rarely viruses
- Causative bacteria include
 - *Streptococcus haemolyticus*
 - *Staphylococcus aureus*
 - *Pneumococcus*
 - *Actinomyces*
 - Less commonly gram-negative bacteria
 - In adults ~ 80% caused by *Streptococcus haemolyticus*; *Staphylococcus aureus* represents sole pathogen in ~ 70% of cases
 - In pediatric ages, ~ 70% caused by α - and β -hemolytic *Streptococcus*
- Mycobacteria
 - *M. tuberculosis*, *M. avium-intracellulare*
 - Mycobacterial infections are rare even in patients with miliary tuberculosis
- Causative fungi include
 - Primarily reported *Aspergillus* species
 - Virtually all affected patients are immunocompromised
 - Other fungi causing thyroiditis include
 - *Coccidioides immitis*, *Histoplasma capsulatum*, *Candida albicans*, *Allescheria boydii*, *Nocardia asteroides*, *Pneumocystis jiroveci* (in patients with AIDS)
 - Rarely, *Cryptococcus* or *Mucor*
- Causative viruses include
 - Cytomegalovirus
 - Occurs in patients with AIDS

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon
 - Tends to develop in immunocompromised, immunosuppressed, or malnourished patients
 - Patients with HIV or AIDS, organ transplant patients on pharmacologic immunosuppression, cancer patients undergoing chemotherapy, patients on immunomodulation therapy for other disorders
 - Not infrequently associated with
 - Concomitant localized infection
 - Part of systemic involvement
 - Spread of infection to thyroid gland via lymphatics and, less commonly, via hematogenous routes
- Age
 - Occurs in any age group
- Sex

- Equal gender distribution

Site

- No specific localization

Presentation

- Fever with swelling and pain in neck region radiating or referred to jaw &/or ear region
- Additional symptoms may include fatigue, dyspnea, dysphagia, and hoarseness
- For acute thyroiditis
 - Not infrequently, history of antecedent or concomitant upper aerodigestive tract infection
- Thyroid gland is warm to hot on palpation

Laboratory Tests

- Patients are usually euthyroid, but clinical evidence of hyperthyroidism or hypothyroidism may occur
- Cultures for microorganisms may be of assistance in diagnosis
 - Microbiologic analysis can be performed on material from fine-needle aspiration

Treatment

- Options, risks, complications
 - Acute and granulomatous thyroiditis
 - Treatment is predicated on diagnosis and identification of causative microbe
 - Once microorganism is identified, appropriate antimicrobial therapy can be initiated
- Surgical approaches
 - Surgical intervention (drainage) may be required in presence of abscess formation

Prognosis

- For bacterial-related acute thyroiditis
 - Excellent prognosis, with most patients experiencing recovery
 - Rarely, recurrence and even death may occur
 - Recurrent acute suppurative thyroiditis may occur secondary to piriform sinus fistula
 - Piriform sinus fistula identified by radiographic evaluation
 - In this setting, thyroiditis usually left-sided
 - Treatment for piriform sinus fistula includes fistulectomy
- Prognosis for fungal infection is poor
 - Generally terminal event in immunocompromised patient
- Prognosis for mycobacterial infection correlates with that of other organ system involvement

MACROSCOPIC

General Features

- **Acute thyroiditis**
 - Gross appearance quite variable, includes focal or diffuse enlargement
 - In some instances, thyroid appears normal
 - Abscess formation can be seen by soft purulent areas
- **Granulomatous thyroiditis**
 - May include soft purulent (caseating) areas, abscess formation, or miliary tubercles

MICROSCOPIC

Histologic Features

- **Acute thyroiditis**
 - Pathologic process may be suppurative or nonsuppurative
 - Focal to diffuse acute inflammatory cell infiltrate (polymorphonuclear leukocytes) with destruction of follicular epithelial cell architecture
 - Areas of abscess formation characterized by dense pool of leukocytes can be seen
 - Areas of necrosis and leukocytic debris may be present
 - Depending on causative microorganism, offending agent may or may not be identifiable by light microscopy
- **Granulomatous inflammation**
 - Classic caseating granulomas may be present in either mycobacterial or fungal infection
 - Include foci of central necrosis surrounded by histiocytic cell reaction with scattered associated multinucleated giant cells
 - In immunocompromised patient
 - Typical granulomatous inflammatory process may not occur in face of mycobacterial or fungal infection
 - Changes of acute thyroiditis may be seen
- Irrespective of causative organism, histologic picture of mycobacterial infection is same

ANCILLARY TESTS

Cytology

- Fine-needle aspiration represents primary diagnostic modality
 - Polymorphonuclear leukocytes are present
 - Microorganisms can be identified by histochemical analysis.

Histochemistry

- Histochemical stains may assist in identification of microorganism
 - Fungal infections: Positive for Grocott methenamine-silver and PAS
 - Mycobacterial infection: Positive for acid-fast bacilli and Ziehl-Neelsen; appear beaded, red, or purple but may be difficult to identify

Immunohistochemistry

- Assist in identification of microorganism (e.g., CMV, HSV1/2)

In Situ Hybridization

- Assist in identification of microorganism (e.g., CMV, HSV1/2)

DIFFERENTIAL DIAGNOSIS

Sarcoidosis

- Multisystem chronic granulomatous disease of unknown etiology
- May involve thyroid as part of systemic process or, rarely, localized to thyroid
- Noncaseating granulomas consisting of epithelioid histiocytes surrounded by mixed inflammatory infiltrate and multinucleated giant cells

Subacute (de Quervain) Thyroiditis

- Granulomatous inflammatory condition of thyroid gland with characteristic clinical and pathologic findings
- Etiology is, in all probability, infectious with strong evidence supporting viral agent

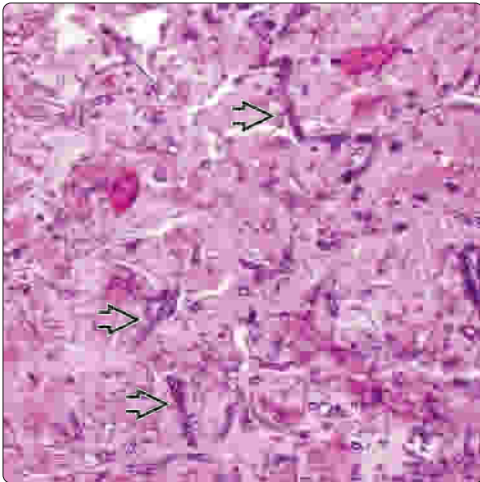
Palpation Thyroiditis

- Traumatically induced lesions caused by vigorous clinical palpation of thyroid gland
- Does not cause abnormalities in thyroid function (hypothyroidism or hyperthyroidism)
- Incidental microscopic finding in thyroid glands resected for other reasons

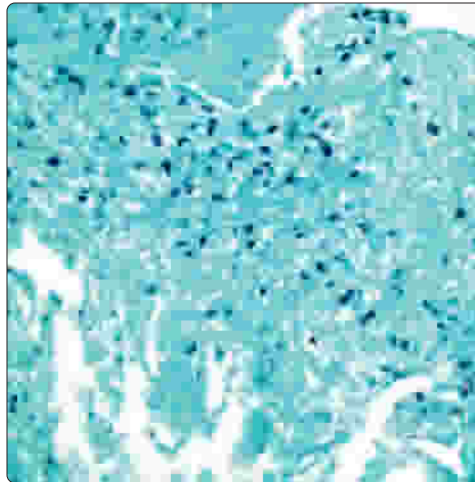
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Fungal Thyroiditis

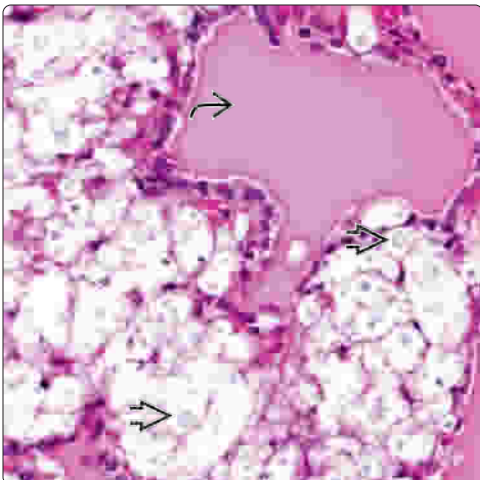


***Pneumocystis jiroveci* Thyroiditis**

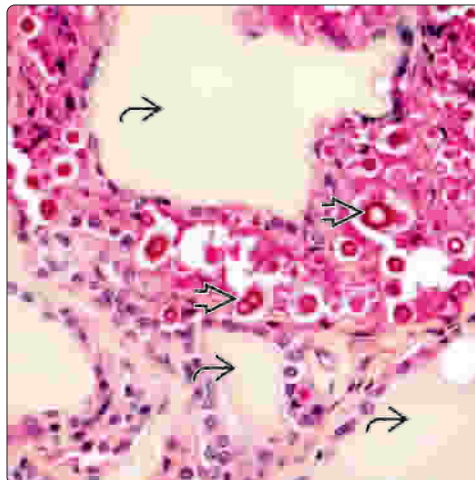


(Left) Mucormycosis may infect the thyroid, causing acute thyroiditis, and is identified by routine staining characterized by haphazardly branched hyphae that, unlike *Aspergillus* species, are broad, irregularly branched, and rarely septated. (Right) *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) may rarely infect the thyroid gland and when present occur in AIDS patients; the organisms identify within foamy exudate, stain black on Grocott methenamine silver, and appear round with cell membrane irregularities.

Cryptococcal Thyroiditis



Cryptococcal Thyroiditis

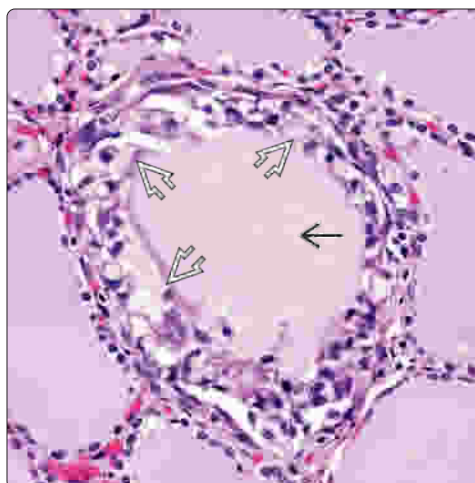


(Left) *Cryptococcus*, a fungus, may rarely infect the thyroid gland. The microorganisms are readily identified in routine staining and are characterized by spherical microorganisms with thickened capsule. (Right) Thyroid follicles surrounded by organisms show characteristic mucicarmine-positive cell walls. Cryptococcal infection typically causes an acute inflammatory infiltrate, but in immunocompromised hosts may be devoid of associated inflammation.

Palpation Thyroiditis



Palpation Thyroiditis



(Left) Palpation thyroiditis is typically an incidental microscopic finding seen in thyroid glands removed for other reasons. It is caused by vigorous palpation, shows replacement of follicular epithelial cells by histiocytes and chronic inflammatory cells, and is surrounded by normal-appearing thyroid parenchyma. (Right) At higher magnification, there is replacement of follicular epithelial cells by histiocytes and chronic inflammatory cells with retention of intrafollicular colloid.

KEY FACTS

TERMINOLOGY

- Microscopic granulomatous foci centered on thyroid follicles thought to result from rupture of follicles due to palpation

ETIOLOGY/PATHOGENESIS

- Often vigorous, repeated manipulation of thyroid gland
- Martial arts (karate, Tang Soo Do, jiu-jitsu, judo)

CLINICAL ISSUES

- Usually nodule present that precipitated palpation in 1st place
 - Prominent in **completion thyroidectomy** specimens
 - Very common in surgically resected thyroid glands
- Very common in surgically resected thyroid glands
- Usually resolves with time

MICROSCOPIC

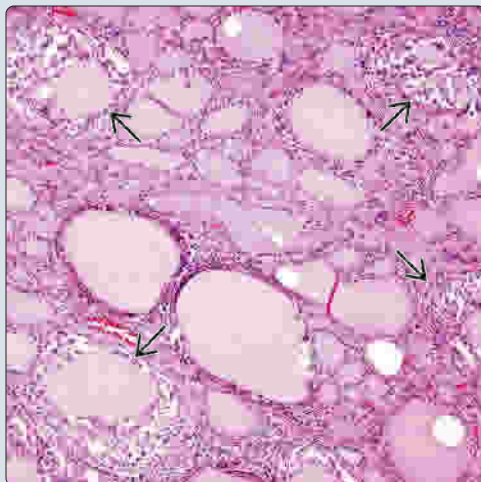
- Widely scattered throughout gland

- Small foci, centered on 1 or few adjacent follicles
- Follicle contains aggregates of foamy histiocytes, few lymphocytes/plasma cells, and occasional multinucleated giant cells
 - Generally no follicular epithelium
 - Called microgranulomas
 - No neutrophils
 - No necrosis

TOP DIFFERENTIAL DIAGNOSES

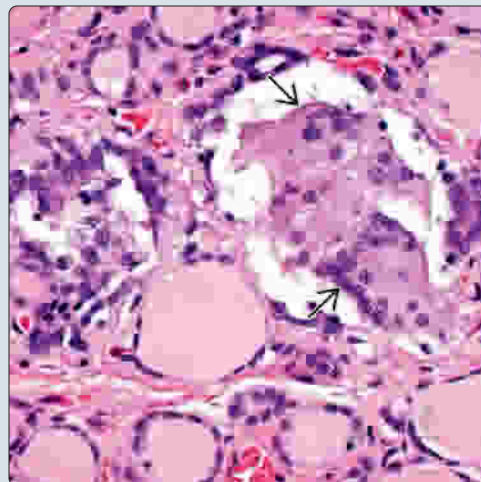
- Chronic lymphocytic (Hashimoto) thyroiditis
- Subacute thyroiditis (de Quervain)
- Infectious thyroiditis
- Sarcoidosis
- Fine-needle aspiration changes

Granulomas of Palpation Thyroiditis

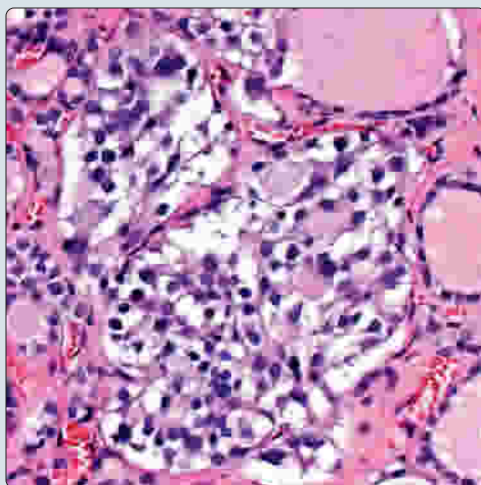


(Left) There are multiple separate microgranulomas centered on a single follicle in this case of palpation thyroiditis. There are scattered, single follicles destroyed with the lumina filled with histiocytes. *(Right)* In this example of palpation thyroiditis, foreign body-type giant cells are noted within the single destroyed follicle. Histiocytes are present but follicular epithelium is absent.

Single Destroyed Follicles With Histiocytes

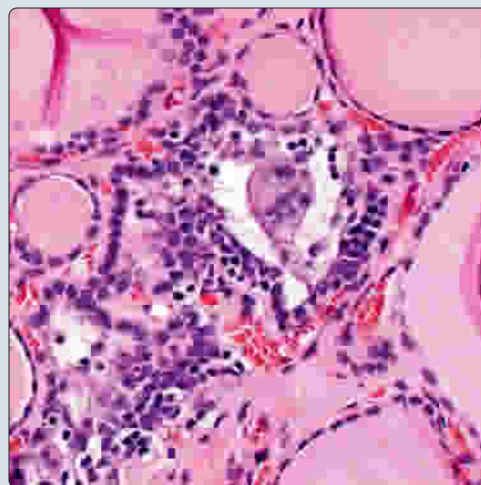


Giant Cells and Histiocytes Replace Follicle



(Left) Two adjacent follicles are destroyed and the follicle outline is now filled with lymphocytes and histiocytes. No residual follicular epithelium is present. *(Right)* These 2 follicles contain giant cells and lymphocytes, an isolated microgranuloma commonly seen in palpation thyroiditis.

Giant Cells With Follicle



TERMINOLOGY

Synonyms

- Multifocal granulomatous folliculitis

Definitions

- Microscopic granulomatous foci centered on thyroid follicles thought to result from rupture of follicles due to palpation

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Pressure-induced damage and rupture of follicles by squeezing during manual examination
 - Palpation
 - Often vigorous, repeated manipulation of thyroid gland preoperatively
 - Identified in thyroids of patients who died while hospitalized vs. patients who died at home
 - Identical findings produced experimentally in dogs whose thyroids were vigorously squeezed
 - Martial arts (karate, Tang Soo Do, jiu-jitsu, judo)
- Possibly related to physiologic alterations in follicular basement membrane (similar to subacute granulomatous thyroiditis)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very common in surgically resected thyroid glands
- Age
 - All ages
- Sex
 - Equal gender distribution

Presentation

- No clinical presentation as signs and symptoms are subclinical if present at all
 - Usually nodule present that precipitated palpation in 1st place

Laboratory Tests

- No change in thyroid function tests

Natural History

- Resolves with time

Treatment

- Options, risks, complications
 - No treatment required

Prognosis

- Palpation thyroiditis is of no clinical significance

MACROSCOPIC

General Features

- No gross findings, although, focal hemorrhage may be seen
- Usually nodule, which prompted palpation

Size

- Microscopic only: 50-1,000 μ m

MICROSCOPIC

Histologic Features

- Widely scattered throughout gland
- Small foci, centered on 1 or few adjacent follicles
- Follicle contains aggregates of foamy histiocytes, few lymphocytes/plasma cells, and occasional multinucleated giant cells
 - Called microgranulomas
 - No neutrophils
 - No necrosis
 - Generally no follicular epithelium
- Ruptured follicles associated with minimal fibrosis
- Much more prominent in **completion thyroidectomy** specimens
- **Important:** Clinically significant disorders are usually present
 - Nodules, neoplasms

DIFFERENTIAL DIAGNOSIS

Chronic Lymphocytic (Hashimoto) Thyroiditis

- Affects entire gland
- 3 components: Oncocytic epithelium, lymphocytes, germinal centers
- Lacks follicle destruction

Subacute Thyroiditis (de Quervain)

- Larger aggregates of follicle-centered granulomas
- Early phase: Neutrophils and histiocytes are present with large areas of involvement
 - Necrosis may be present, although not frequent
- Later stages: Fibrosis is prominent with foreign body-type giant cells

Infectious Thyroiditis

- Specifically tuberculosis, fungal organisms, syphilis
- Much more prominent granulomatous inflammation affecting more tissue
- May have necrosis (caseating granuloma)
- Organisms can be identified with special studies (histochemistry, immunofluorescence, immunohistochemistry)

Sarcoidosis

- Interstitial small, tight, compact granulomas
- Asteroid bodies and Schaumann bodies
- Usually part of systemic disease

Fine-Needle Aspiration Changes

- History of fine-needle aspiration
- Hemosiderin, erythrocytes, and reactive fibrosis
- Linear process, often centered on nodule/tumor

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KEY FACTS

TERMINOLOGY

- Self-limited inflammatory condition characterized by epithelioid histiocytes, multinucleated giant cells, and acute inflammatory cells
 - Requires clinicopathologic correlation with known systemic disease

CLINICAL ISSUES

- Female >> male (3.5:1)
- Wide range; peak: 5th decade
- Entire gland usually involved
- Painful thyroid gland is most common symptom
- Frequently presents with hyperthyroidism
- Spontaneous return to normal function in most patients within 12 months
- Thyroid function varies during disease arc
- Supportive Western therapy, perhaps combined with Chinese herbal medicines

IMAGING

- Very low thyroid ^{131}I uptake in clinically hyperthyroid patient

MICROSCOPIC

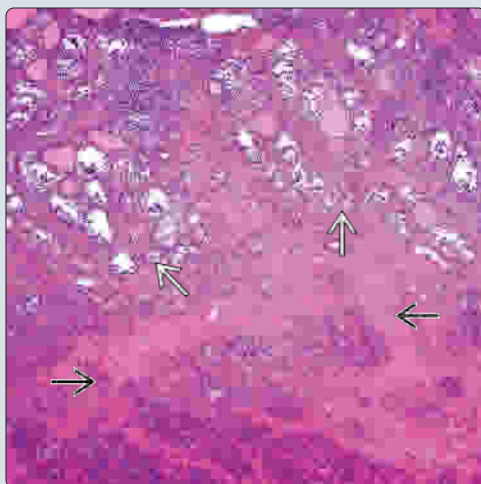
- Asymmetric enlargement with ill-defined nodules
- Inflammatory process unevenly affects entire gland
- Topographic and temporal variation of histology depending on stage
 - **Acute stage:** Folliculocentric, follicular damage, loss of epithelium and colloid, replaced by neutrophils
 - **Mid stage:** Chronic inflammation, epithelioid histiocytes, multinucleated giant cells, fibrosis
 - **Resolution stage:** Follicular tissue is regenerated, restoring normal structure

TOP DIFFERENTIAL DIAGNOSES

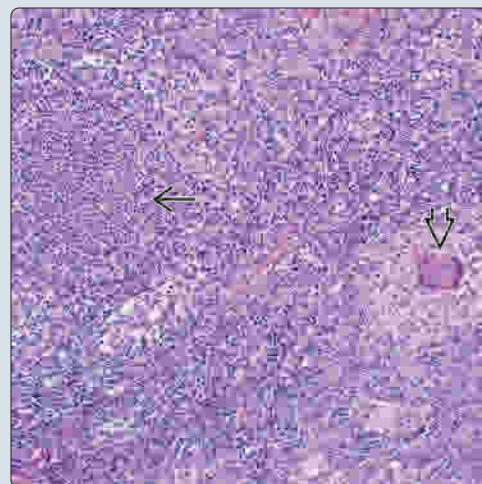
- Subacute lymphocytic thyroiditis, granulomatous thyroiditis, sarcoidosis, palpation thyroiditis, Riedel thyroiditis

Fibrosis With Acute Inflammation

(Left) A nodule of fibrosis is immediately adjacent to a zone of active inflammation. The coexistence of temporally different zones (fibrosis vs. active disease) is due to migration of the inflammatory process to previously unaffected regions. (Right) Two of the features seen in subacute thyroiditis are the presence of neutrophils often arranged in a microabscess within a destroyed follicle and the presence of giant cells and epithelioid histiocytes.

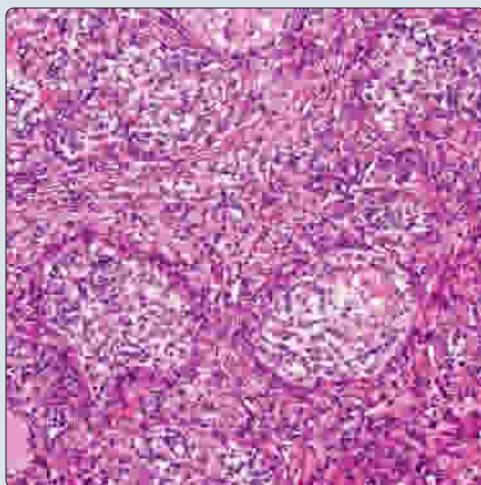


Microabscess and Giant Cells

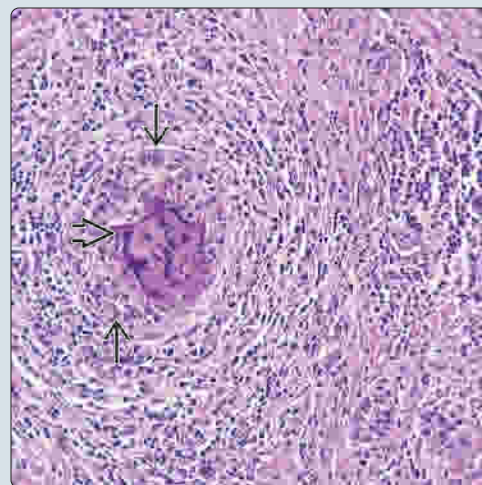


Partially Destroyed Follicles

(Left) Multiple follicles are affected by a mixed inflammatory infiltrate, including histiocytes and neutrophils. There is a background of interfollicular fibrosis. This early stage shows the folliculocentric process. (Right) The mixed inflammatory infiltrate shows lymphocytes surrounding a destroyed follicle filled with epithelioid histiocytes and multinucleated giant cells with neutrophils. Fibrosis is also seen.



Giant Cells and Acute Inflammatory Cells



TERMINOLOGY

Abbreviations

- Subacute granulomatous thyroiditis (SGT)

Synonyms

- de Quervain thyroiditis (named after Fritz de Quervain, Swiss surgeon)
- Subacute thyroiditis
- Granulomatous thyroiditis
- Painful subacute thyroiditis, postviral thyroiditis, giant cell thyroiditis, subacute nonsuppurative thyroiditis, pseudotuberculous thyroiditis, struma granulomatosa

Definitions

- Self-limited inflammatory condition characterized by epithelioid histiocytes, multinucleated giant cells, and acute inflammatory cells (at certain times in disease development)
 - Requires clinicopathologic correlation with known systemic disease
 - Granulomatous inflammation can be seen in patients with tuberculosis, fungal infections, sarcoidosis

ETIOLOGY/PATHOGENESIS

Infectious

- Systemic viral infection most common
 - Common prodromal signs and symptoms
 - Intrathyroidal activated T-cytotoxic cells with interferon γ (+) lymphocytes
 - Incidence highest in summer months, coincident with enteroviral infections
 - Associated with mumps, influenza, Coxsackie adenovirus, and measles epidemics
 - However, significant number of patients do not have viral infection
- Develops after antiviral therapy, specifically interferon

Inherited

- Genetic predisposition suggested
 - Increased frequency in patients with HLA-B35 haplotype

Autoimmune

- Possible autoimmune component, as there are thyroid autoantibodies in few patients

CLINICAL ISSUES

Epidemiology

- Incidence
 - Incidence ~ 5 per 100,000 population per year
 - Suggested seasonal increase in spring and summer
- Age
 - Wide range; peak: 5th decade
 - Rare in children
- Sex
 - Female >> male (3.5:1)

Site

- Entire gland usually involved
 - May be localized to 1 lobe or a distinct nodule

Presentation

- Prodrome heralds disease
 - Low-grade fever, myalgias, fatigue, sore throat
- Painful thyroid gland is most common symptom
 - SGT is most common cause of painful thyroid
 - May radiate to jaw
 - Tender to palpation
 - Some patients may not have pain or tenderness
- Frequently presents with hyperthyroidism
 - Rarely, may present with thyroid storm
- Become hypothyroid in ensuing weeks to months
- Spontaneous return to normal function in most patients within 12 months
 - ~ 7% have persistent hypothyroidism
- May have other symptoms, including
 - Dysphagia, arthralgia, tremor, excessive sweating, weight loss

Laboratory Tests

- Thyroid function varies during disease arc
 - **Early phase:** May be hyperthyroid due to follicle destruction and release of hormone
 - TSH is suppressed; T4 and T3 are elevated
 - **Mid phase:** Become hypothyroid after follicles are destroyed
 - **Late phase:** Regain euthyroid after disease resolution
 - Few patients may have transient elevation of antibodies to thyroglobulin or thyroperoxidase
- C-reactive protein and erythrocyte sedimentation rate are usually elevated

Natural History

- Self-limited disease
- Resolves in several months
- Rarely, may recur years later

Treatment

- Options, risks, complications
 - Supportive Western therapy
 - Nonsteroidal anti-inflammatory drugs
 - Aspirin contraindicated as it displaces thyroid hormone from thyroid-binding globulin
 - Steroids (such as prednisone) for more severe symptoms
 - β -blocking agents (like propranolol) if thyrotoxicosis is present
 - Chinese herbal medicines (especially when combined with Western medicine) may improve clinical symptoms and signs, reduce relapse rate, and alleviate side effects of hormones
 - Surgery is unnecessary

Prognosis

- Self-limiting disease
 - Resolves within several months
- Infrequently (~ 2%), recurrence may develop, often years after initial episode
- ~ 7% of patients remain permanently hypothyroid
- Rarely, chronic lymphocytic thyroiditis or Graves disease may develop

Subacute Granulomatous Thyroiditis (de Quervain)

IMAGING

Radiographic Findings

- Best radiographic clue is very low thyroid ^{131}I uptake in clinically hyperthyroid patient
 - Acute phase: Radioactive iodine uptake is very low (< 1% at 24 hours)
 - Uptake will improve with recovery

Ultrasonographic Findings

- **Acute** phase: Hypoechoic with nonechoic regions secondary to inflammation and tissue damage
- **Recovery** phase: Isoechoic with slightly increased vascularity
- By grayscale US, most cases show lava flow: Heterogeneous diffusely or focally marked hypoechoic areas

MACROSCOPIC

General Features

- Asymmetric enlargement (usually 2x) with vague nodularity
- Tan to yellow-white, ill-defined nodules
- Somewhat firm consistency

MICROSCOPIC

Histologic Features

- Inflammatory process unevenly affects entire gland (65% bilateral)
 - Nodular, even though whole gland is affected
 - Few cases have solitary nodule
- Topographic and temporal variation of histology depending on stage
 - Inflammatory infiltrate composed of lymphocytes, plasma cells, foamy histiocytes, epithelioid histiocytes, multinucleated giant cells, neutrophils
 - Variable background of fibrosis
 - Zones of active inflammation coexist with areas of fibrosis as inflammatory process migrates to previously unaffected parenchyma
- **Early stage** (acute; hyperthyroidism)
 - Folliculocentric, with follicular damage and loss of epithelium and colloid
 - Groups of follicles filled with mixed inflammatory cells
 - Neutrophils predominant, occasionally forming microabscesses
 - Inflammation (predominantly lymphohistiocytic) expands into adjacent interfollicular zones
- **Mid stage** (hypothyroidism)
 - Chronic inflammation
 - Lymphocytes, plasma cells
 - Epithelioid and nonepithelioid macrophages and multinucleated giant cells (histiocytic)
 - Giant cells adjacent to or within disrupted follicles
 - Giant cells may surround and engulf residual colloid
 - Well-formed granulomata are not seen
 - Variable degrees of fibrosis
 - Follicular epithelium may be difficult to detect, as it has been destroyed
- **Late stage** (resolution; recovery)
 - Fibrosis replaces destroyed follicles

- Follicular tissue is regenerated, restoring normal structure
- Fibrosis and inflammatory infiltrate resolves

ANCILLARY TESTS

Cytology

- FNA seldom requested, except in pain-free patients
- Mixture of lymphocytes, plasma cells, foamy and epithelioid histiocytes, multinucleated giant cells
- Neutrophils may be prominent in early phase
- Giant cells may contain colloid fragments
- Colloid and degenerated follicular epithelial cells usually scant (especially early phase)
 - Oncocytic follicular cells are absent

DIFFERENTIAL DIAGNOSIS

Subacute Lymphocytic Thyroiditis

- Also called postpartum lymphocytic thyroiditis
 - 1-6 months after delivery
- Painless and clinically silent
- Thought to be autoimmune mediated
 - Perhaps variant of Hashimoto thyroiditis
- Lymphoid follicles with germinal centers
 - Not seen in SGT

Granulomatous Thyroiditis

- Well-formed granuloma
 - Ring of epithelioid histiocytes around area of central caseating necrosis
- Infectious agents should be excluded
 - Special studies for mycobacteria &/or fungi

Sarcoidosis

- Usually found in interstitium
 - Not folliculocentric
- Small, compact aggregates of epithelioid histiocytes
- Giant cells may be present
- Necrosis tends to be absent

Palpation Thyroiditis

- Affects 1 to few follicles
 - May be distributed throughout gland
- No neutrophils
- Multinucleated giant cells constant feature

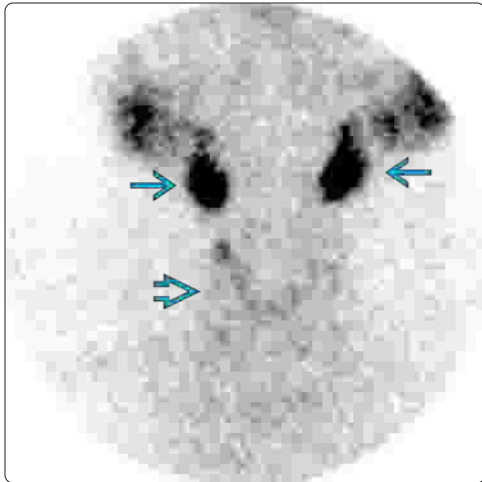
Riedel Thyroiditis (IgG4 Sclerosing Disease)

- Tumefactive, dense storiform fibrosis with obliterative vasculitis, heavy lymphoplasmacytic infiltration
- > 40% IgG4/IgG(+) cells and elevated IgG4(+) plasma cells

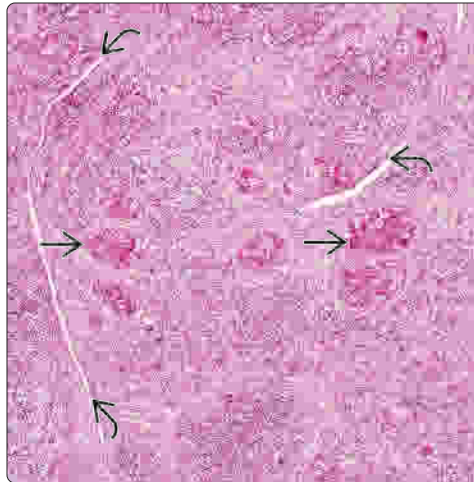
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Low ^{131}I Uptake Scintigraphy

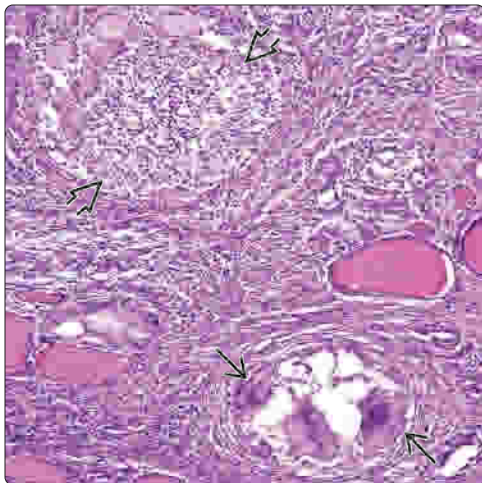


Dilated Lymphatics and Giant Cells

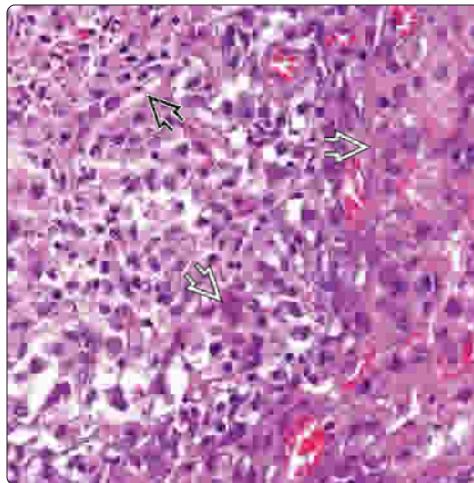


(Left) One of the best radiographic clues to the diagnosis is a very low thyroid radioactive iodine uptake (< 1% at 24 hours) in a clinically hyperthyroid patient (acute phase). This anterior thyroid scan shows nearly absent thyroid activity with normal salivary activity. (Right) This whole area is affected by the inflammatory reaction. Fibrosis is noted, along with dilated lymphatics. There are groups of histiocytes filling destroyed follicles, with multinucleated giant cells engulfing colloid.

Various Phases of Development

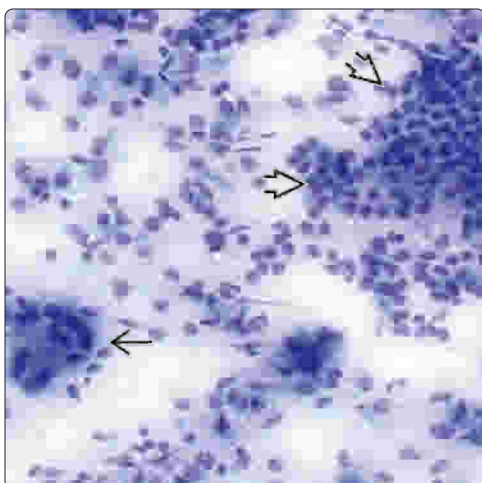


Follicle-Centric Destruction

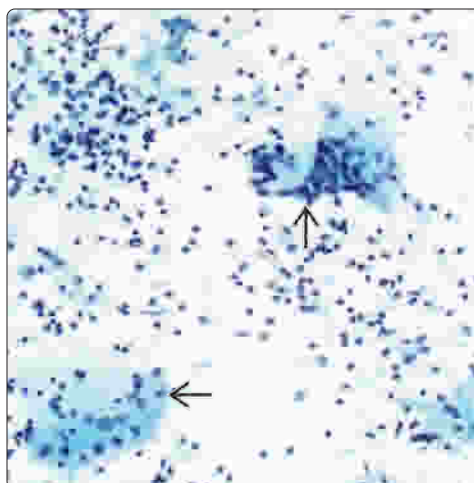


(Left) A topographic separation of temporally distinctive processes is shown: Acute stage shows a destroyed follicle filled with neutrophils (microabscess); mid stage shows multinucleated giant cells within a follicle. Fibrosis is noted between the 2 regions. (Right) High power shows a follicle with neutrophils and debris surrounded by foamy histiocytes and epithelioid histiocytes. No colloid or follicular epithelium is present.

Giant Cells and Epithelioid Histiocytes



Giant Cells and Inflammatory Cells



(Left) There are epithelioid histiocytes and multinucleated giant cells in this smear. Note the follicular epithelial cells in the background. (Right) There are lymphocytes, epithelioid histiocytes, and multinucleated giant cells in this example of subacute thyroiditis.

KEY FACTS

TERMINOLOGY

- Hashimoto thyroiditis is characterized by goiter and elevated circulating thyroid antibodies often associated with hypothyroidism due to thyroid destruction by autoimmune process &/or presence of thyroid-stimulating hormone-blocking antibodies

CLINICAL ISSUES

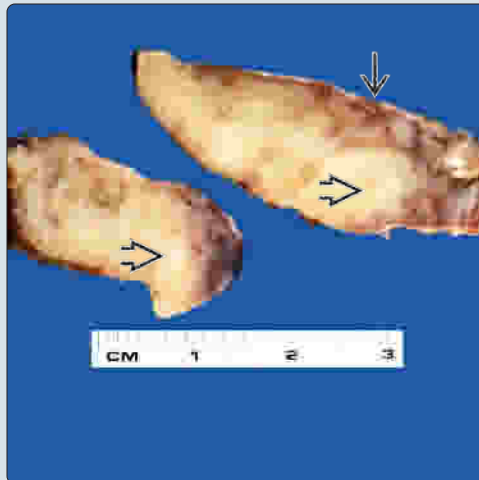
- **Classic type**
 - Many patients present with no signs or symptoms with diagnosis made on basis of
 - Laboratory tests of thyroid function
 - Screening done for thyroid antibodies
 - Patients may present with mass lesion (goiter)
- **Fibrous variant**
 - Symptoms of large goiter that may produce dysphagia and dyspnea
 - Suggestion that fibrosing variant is part of spectrum of IgG₄-related diseases but not confirmed

MICROSCOPIC

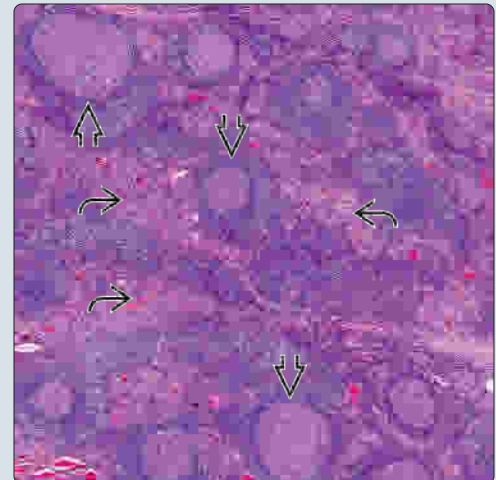
- **Classic type**
 - At low magnification, lobules or nodules are seen separated by fibrous tissue
 - Diffuse involvement of thyroid gland
 - Thyroid atrophy includes presence of small follicles with limited to absent colloid formation
 - Mature lymphocytic cell and plasma cell infiltrate ± germinal centers
 - Oncocytic cytoplasmic change of follicular epithelial cells
- **Fibrous variant**
 - Presence of nodular or lobular pattern of growth with associated dense fibrosis; fibrosis is keloid-like
 - Inflammatory cell infiltrate includes mature lymphocytes as well as plasma cells
 - Follicular epithelial changes include follicular atrophy, oncocytic cytoplasmic changes

Nodular and Fibrotic Thyroid Gland

(Left) Thyroid resection from a patient with Hashimoto thyroiditis shows diffuse involvement of the gland with replacement of the normal thyroid parenchyma by tan to light brown tissue that on cut section shows a nodular appearance. Residual grossly normal-appearing thyroid tissue is present at the periphery. (Right) Histologically, there is diffuse involvement of the thyroid by a prominent lymphocytic infiltrate, including associated germinal centers present in and around the residual thyroid parenchyma.

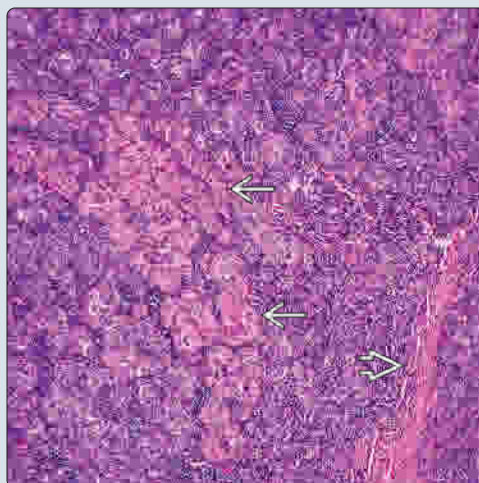


Diffuse Thyroid Involvement

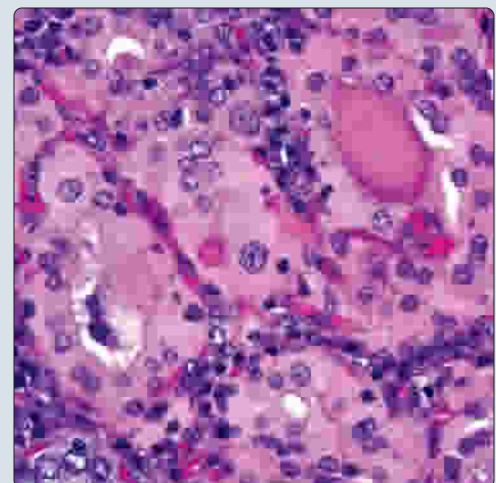


Lymphocytic Infiltrate, Oncocytic Cells, & Fibrosis

(Left) Histologic features associated with Hashimoto thyroiditis include prominent lymphocytic and plasma cell infiltrate, presence of oncocytic cytoplasmic changes in follicular epithelial cells and fibrosis. (Right) At higher magnification, the oncocytic follicular cells are characterized by prominent granular eosinophilic appearing cytoplasm with associated nuclear enlargement and variable degree of chromatin clearing.



Oncocytic Follicular Cells



TERMINOLOGY

Abbreviations

- Hashimoto thyroiditis (HT)

Synonyms

- Autoimmune thyroiditis (classic form) or autoimmune thyroid disease (AITD), "classic" Hashimoto thyroiditis, struma lymphomatosa, lymphadenoid goiter

Definitions

- HT is characterized by goiter and elevated circulating thyroid antibodies often associated with hypothyroidism due to thyroid destruction by autoimmune process &/or presence of thyroid-stimulating hormone-blocking antibodies

ETIOLOGY/PATHOGENESIS

Genetic

- Major histocompatibility complex (MHC) class II genes encode products that delete autoreactive T cells, select for presentation of autoantigenic peptides or activate suppressor T cells
 - Other MHC genes potential effects on antigen presentation
- Epidemiological data, including family and twin studies, point to strong genetic influence in development of AITD

Nongenetic

- Infectious agents may release autoantigens, alter expression of surface molecules, directly affect immune system or contain immunologic sequences (epitopes) that mimic autoantigens
- Dietary factors
 - Iodide may enhance immunogenicity of thyroglobulin, alter thyroid-cell function or form toxic metabolites with oxygen
 - Vitamin D deficiency may predispose to development of autoimmune disease through effects on dendritic cells and T cells
- Hormones
 - Estrogens enhance most immune responses
 - Glucocorticoids, androgens suppress immune responses
- Drugs
 - Lithium, interferon, interleukin and some other cytokines exacerbate or promote progression of autoimmune thyroiditis
- AITD may appear as part of immune reconstitution syndrome after bone marrow transplantation from affected donor, alemtuzumab (monoclonal antibody against CD52) treatment or highly active antiretroviral treatment for HIV infection
- Familial association: Up to 5% of first-degree relatives with chronic lymphocytic (Hashimoto) thyroiditis have antithyroid antibodies

Autoimmunity

- Patients with HT are at greater risk of other coexisting autoimmune diseases, including insulin dependent diabetes mellitus, Addison disease, autoimmune oophoritis, hypoparathyroidism, and hypophysitis

- HT is well-recognized component of autoimmune polyglandular syndromes (heterogeneous group of rare diseases characterized by autoimmune activity against > 1 endocrine organ)
- HT and Graves disease share common features including
 - Aggregation of both conditions in same families or within the same thyroid gland
 - Cases of identical twins in which one twin has HT and other has Graves disease
 - Lymphocytic infiltration and various immunoglobulins found within thyroid in both disorders
 - Graves disease may evolve into HT with hypothyroidism, and rarely, chronic lymphocytic (Hashimoto) thyroiditis (± hypothyroidism) may evolve into Graves disease with hyperthyroidism
- In spite of shared features, sufficient differences (genetic, clinical, immunologic, pathologic) to consider HT and Graves as distinctly different

CLINICAL ISSUES

Epidemiology

- Incidence
 - AITD includes several different clinical entities most important include
 - Chronic lymphocytic (Hashimoto) thyroiditis (HT)
 - Considered most common autoimmune disease
 - Chronic atrophic thyroiditis
 - In addition, several other clinicopathologic entities are recognized
 - Fibrous variant (occurs in ~ 10% of cases of HT), IgG₄-related thyroiditis, juvenile form, painless thyroiditis (sporadic or postpartum), hashitoxicosis
- Age
 - **Classic type**
 - Occurs over wide range
 - Frequency increases with age
 - Most common cause of goiter and acquired hypothyroidism in children and adolescents in iodide-replete areas
 - **Fibrous variant**
 - Occurs in older patients
 - Suggested that fibrosing variant is part of spectrum of IgG₄-related diseases (IgG-RD) but not unequivocally confirmed
 - Designation IgG₄-related thyroiditis being suggested as distinct from fibrous variant of chronic lymphocytic (Hashimoto) thyroiditis
- Sex
 - **Classic type**
 - Female >>> male (10:1)
 - **Fibrous variant**
 - Male > female

Site

- No specific localization or lateralization

Presentation

- **Classic type**
 - Wide variation in clinical features
 - In some patients, enlarged thyroid only clinical manifestation of autoimmune thyroiditis

- In many patients, clinical evidence of hypothyroidism present
- Many patients present with no signs or symptoms, with diagnosis made on basis of
 - Laboratory tests of thyroid function
 - Screening done for thyroid antibodies
 - Incidental finding in thyroid glands surgically excised for other reasons
- Patients may present with mass (goiter)
 - Typically there is bilateral diffuse enlargement of thyroid
 - Infrequently, dominant mass lesion confined to 1 lobe of thyroid may be seen simulating neoplastic proliferation
- **Fibrous variant**
 - Patients present with symptoms of large goiter that may produce dysphagia and dyspnea

Laboratory Tests

- **Classic type**
 - Laboratory evidence of hypothyroidism may include
 - Overt hypothyroidism including high serum TSH levels, low serum free thyroxine (T4) levels, possibly decreased free triiodothyronine (T3) although latter may be normal
 - Subclinical hypothyroidism including high serum TSH levels and normal serum free T4 levels
 - Laboratory evidence of autoimmune thyroiditis includes circulating antibodies to
 - Thyroglobulin
 - Thyroid peroxidase (microsomal antigen)
 - Other components of thyroid tissue may serve as autoantigens including thyrotropin (TSH) receptor and, commonly, sodium/iodide cotransporter and pendrin
 - With progression of disease, patients who are not hypothyroid at presentation may develop evidence of hypothyroidism at later time
 - Patients may be euthyroid
 - Rarely patients are hyperthyroid
- **Fibrous variant**
 - Patients often present with severe hypothyroidism
 - High titers of antithyroglobulin antibodies, elevated serum TSH levels

Treatment

- Options, risks, complications
 - T4 (thyroxine) therapy is treatment of choice for all patients with hypothyroidism (overt or subclinical)
 - Immunosuppressive (corticosteroid) therapy may result in regression of thyroid enlargement and decrease in thyroid antibody levels
 - Appropriate therapy for patients who are euthyroid but have enlarged glands (goiter) remains uncertain
 - Complications of thyroxine therapy limited to iatrogenic thyrotoxicosis
- Surgical approaches
 - Surgery can be used in patients who do not respond to thyroxine therapy &/or who have continued enlargement (\pm local symptoms) of thyroid gland

Prognosis

- Generally considered to be good
- Complications include potential development of malignant neoplasm, including
 - Hematolymphoid malignancy (lymphoma or leukemia); follicular epithelial-derived tumors (papillary thyroid carcinoma, follicular carcinoma)

IMAGING

Radiographic Findings

- Ultrasound: Variety of patterns may be seen including normal, glandular enlargement, or diffuse abnormality with heterogeneous echogenicity
- T2WI MR shows areas of increased signal intensity
- In fibrous variant, gland may appear atrophied and fibrotic, resulting in heterogeneous echotexture

MACROSCOPIC

General Features

- **Classic type**
 - Symmetrically (diffusely) enlarged gland
 - Firm consistency, pale in color and characterized by prominent multilobulated appearance; lobules tend to bulge from cut surface and are separated by fibrous tissue
 - Diffuse thyroid enlargement, as compared to single dominant mass, assists in decreasing clinical suspicion for neoplastic proliferation
 - Thyroid not adherent to surrounding structures
 - Pyramidal lobe may be prominent
- **Fibrous variant**
 - Diffusely enlarged, firm to hard, pale tan-appearing thyroid characterized by
 - Presence of fibrosis and prominent lobular appearance
 - Thyroid glands may weigh as much as ≥ 200 g
 - Thyroid not adherent to surrounding structures

MICROSCOPIC

Histologic Features

- **Classic type**
 - At low magnification, lobules or nodules are seen separated by fibrous tissue
 - Diffuse involvement of thyroid gland
 - Thyroid atrophy includes presence of small follicles with limited to absent colloid formation
 - Inflammatory cell infiltrate
 - Primarily composed of mature lymphocytes with admixed mature plasma cells distributed within and around lobules
 - Often prominent germinal centers are present
 - T cells predominate over B cells
 - Macrophages and giant cells may be present
 - Fibrosis within and around follicles
 - Interlobular fibrosis gives gland a nodular appearance
 - Amount of fibrosis usually scanty with slight to moderate thickening in interlobular septa
 - Fibrosis not usually extensive as seen in fibrous variant or as identified in Riedel thyroiditis

- Oncocytic cytoplasmic change of follicular epithelial cells characterized by
 - Eosinophilic granular-appearing cytoplasm
 - Nuclear enlargement
 - Clear to coarse-appearing chromatin
 - Nuclei retain round appearance
 - Prominent nucleoli
- Additional changes that can be seen include
 - Squamous metaplasia (more common in fibrous variant)
 - Intrathyroidal cysts lined by squamous or ciliated respiratory epithelial cells are usually incidentally identified but may attain fairly large sizes, often multifocal and bilateral
 - Predominantly lined by squamous epithelium; columnar cell (respiratory-type) epithelium can be seen, possibly containing goblet cells
 - May be bordered by lymphocytic infiltrate suggesting branchial cleft cysts
 - Similar cysts can be seen in absence of thyroiditis
- **Fibrous variant (advanced lymphocytic thyroiditis)**
 - Presence of nodular or lobular pattern of growth with associated dense fibrosis
 - Fibrosis is keloid-like with irregular broad bands of acellular fibrous tissue coursing in and around remnant of thyroid parenchyma; fibrosis does not extend outside gland
 - Chronic inflammatory cell infiltrate can be seen within fibrotic tissue
 - Mature lymphocytic infiltrate ± germinal centers
 - Inflammatory cell infiltrate includes mature lymphocytes as well as plasma cells
 - Follicular epithelial changes include follicular atrophy & oncocytic cytoplasmic changes; squamous metaplasia may be prominently seen

ANCILLARY TESTS

Cytology

- **Classic type**
 - Usually cellular consisting of mixed population of follicular cells with oncocytic cytoplasm (so-called Hürthle cells), mature lymphocytes and plasma cells with minimal to absent colloid
- **Fibrous variant**
 - Due to marked fibrosis, aspiration generally yields very little material

Immunohistochemistry

- B cells and plasma cells exhibit κ and λ staining (i.e., lack light chain restriction)

Genetic Testing

- Absence of *BRAF* mutation
- Presence of *RET/PTC* rearrangements reported
 - From practical perspective, absence of diagnostic nuclear features for papillary thyroid carcinoma preclude this diagnosis

DIFFERENTIAL DIAGNOSIS

Nonspecific Chronic Lymphocytic Thyroiditis

- Non-mass-forming, scattered but limited foci of lymphocytic infiltrate, typically absence of oncocytic cytoplasmic changes of follicular cells, absence of laboratory evidence of abnormal thyroid function

Non-Hodgkin Malignant Lymphoma

- Characterized by features not present in HT including
- Effacement of thyroid parenchyma with
 - Destruction and effacement of thyroid parenchyma
 - Monomorphic malignant cellular infiltrate (majority of B-cell origin)
 - Presence of lymphoepithelial lesions characterized by colonization of thyroid follicles by neoplastic cells
 - Cellular infiltrate often spills out into perithyroidal soft tissues (not confined to thyroid gland)

Papillary Thyroid Carcinoma

- Constellation of diagnostic nuclear features identified which are absent in HT

Riedel Disease (Invasive Fibrous Thyroiditis)

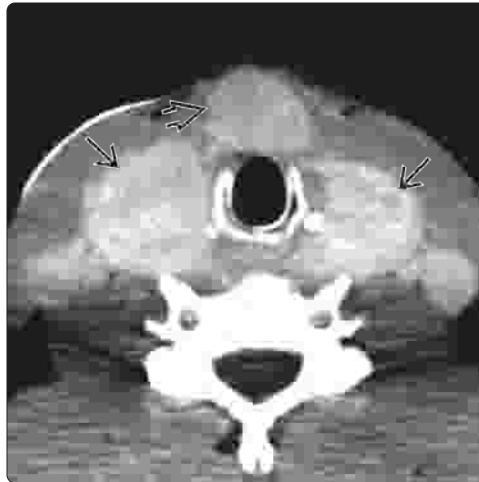
- Differential diagnosis with fibrous variant of lymphocytic thyroiditis
- Fibrosis outside thyroid gland often adherent to surrounding structures
- Lacks high titers of antithyroglobulin antibodies

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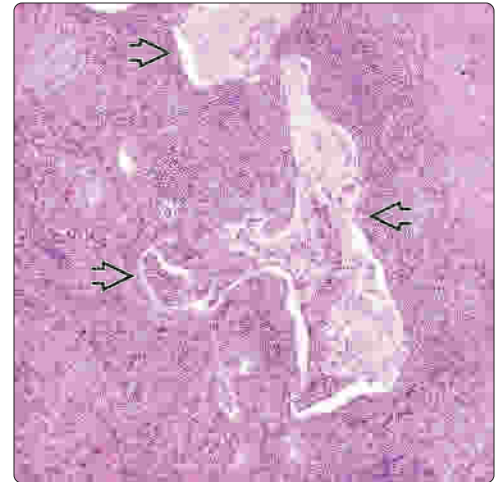
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Imaging Findings in HT

(Left) Axial CECT in a patient with Hashimoto thyroiditis shows diffuse enlargement of both thyroid lobes [B] as well as the pyramidal lobe [C]. (Right) Cysts [D] may be present focally in the setting of Hashimoto thyroiditis. The cysts are usually incidental findings appearing small and indistinct with associated lymphocytic infiltrate (lymphoepithelial cysts), but cysts occasionally may be large, representing a dominant lesion.

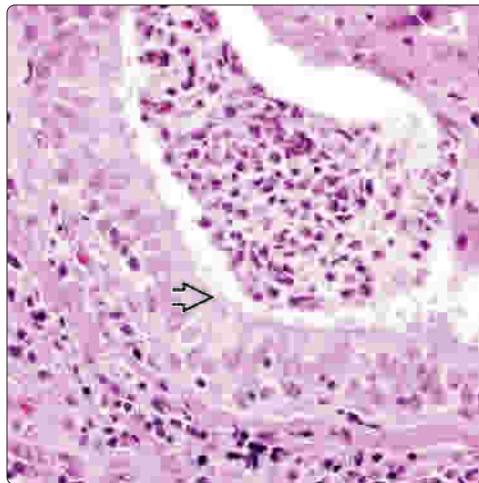


Intrathyroidal Epithelial Cysts

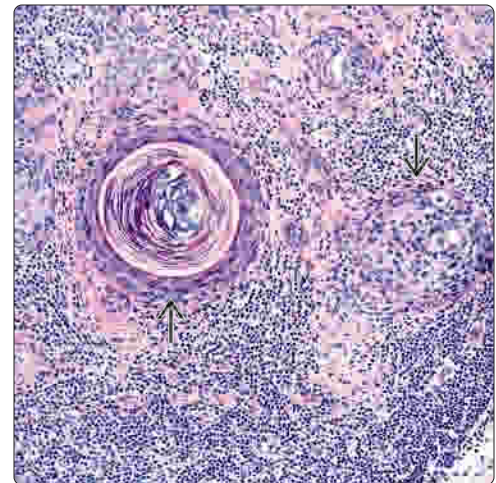


Intrathyroidal Epithelial Cysts

(Left) The cyst is lined by columnar cell epithelium, including cilia [B]. More often, the cysts seen in Hashimoto thyroiditis are predominantly lined by squamous epithelium composed of one or multiple layers of cells (not shown). (Right) Another feature that can be identified in the setting of Hashimoto thyroiditis includes the presence of squamous metaplastic foci as seen here. These foci may appear solid or cystic [B] and may be larger, forming intrathyroidal squamous cell-lined cysts (not shown).

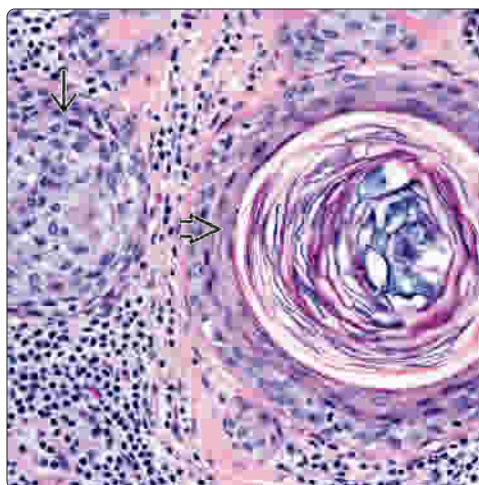


Squamous Metaplasia

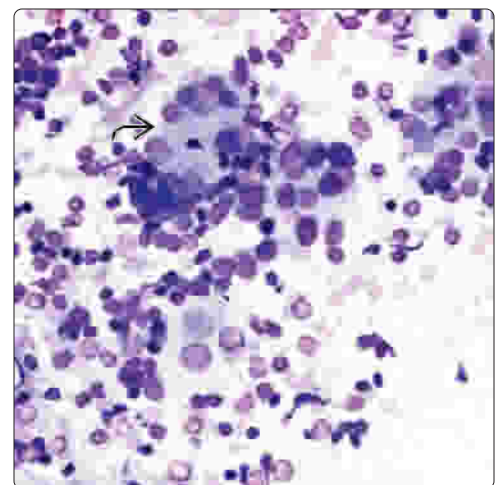


Squamous Metaplasia

(Left) At higher magnification, the squamous metaplastic foci may be nonkeratinizing [B] or keratinizing [B], the latter characterized by overt keratin formation and keratohyaline granules. (Right) Fine-needle aspiration specimen in Hashimoto thyroiditis shows a mixed lymphoplasmacytic cell infiltrate surrounding and partially overrunning clusters of follicular epithelial cells [B] characterized by oncocytic cytoplasmic changes, nuclear enlargement, and variable nuclear pleomorphism.



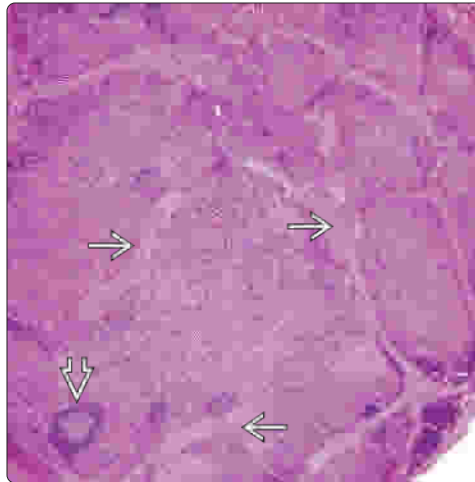
Fine-Needle Aspiration



Fibrous Variant

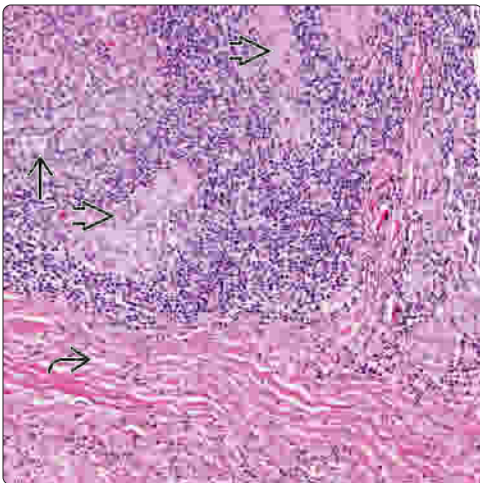


Fibrous Connective Tissue Bonds

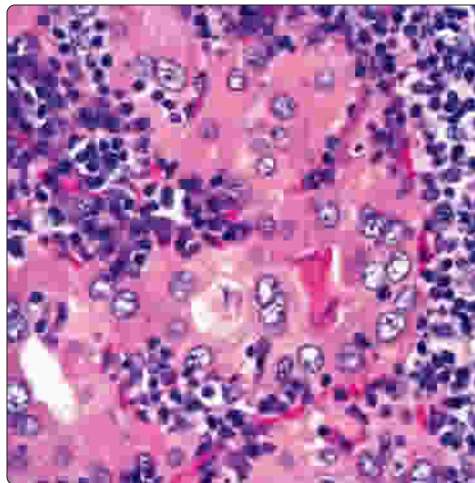


(Left) Fibrous variant of Hashimoto thyroiditis (advanced lymphocytic thyroiditis) includes a diffusely enlarged, firm to hard gland with fibrosis and nodular appearing parenchyma. Due to fibrosis, aspiration generally yields very little material for diagnosis. **(Right)** Fibrous variant of Hashimoto thyroiditis includes fibrous bands creating a nodular appearance with lymphocytic infiltrate including germinal centers that overruns the thyroid tissue. Unlike Riedel disease, the fibrosis does not involve extrathyroidal tissues.

Keloid-Like Collagen

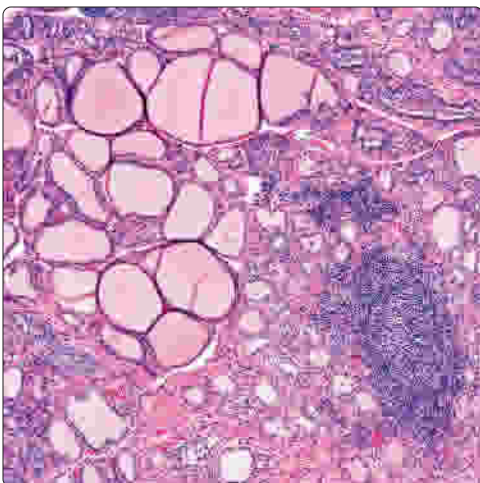


Oncocytic Metaplasia

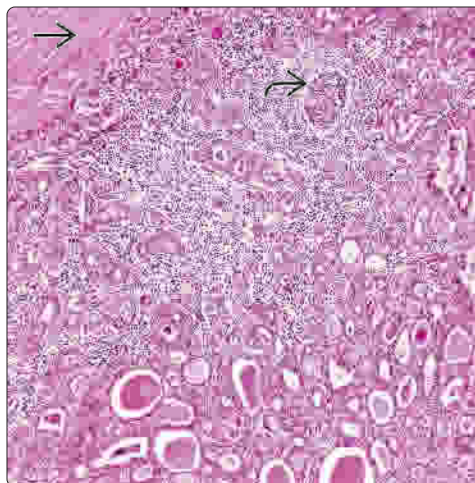


(Left) Fibrous variant shows keloid-like fibrosis with atrophic changes of follicular epithelium that is overrun by a lymphocytic infiltrate; a portion of a germinal center is present. In contrast to the fibrosis in Riedel disease, which extends outside the thyroid, the fibrosis in the fibrous variant of HT is confined within the thyroid. **(Right)** The follicular epithelial cells in the fibrous variant also include brightly eosinophilic (oncocyte) and granular-appearing cytoplasm, associated enlarged nuclei and chromatin clearing.

Focal Lymphocytic Thyroiditis



Simulating Lymph Node Parenchyma



(Left) Nonspecific lymphocytic thyroiditis, a rather common finding, shows limited (not diffuse) lymphocytic infiltrate without alterations of the thyroid follicular cells. **(Right)** A peripherally situated nodular focus composed of lymphocytic cells with germinal centers surrounded by fibrous tissue may simulate features of a lymph node. The absence of a subcapsular sinus and continuity/proximity to the gland proper should preclude misdiagnosis as metastatic carcinoma.

Graves Disease (Diffuse Hyperplasia)

KEY FACTS

TERMINOLOGY

- Autoimmune disorder characterized by excessive production of thyroid hormone and diffuse thyroid enlargement

CLINICAL ISSUES

- Female >> male (7-10:1)
- Generalized manifestations of hyperthyroidism
- Mild to moderate goiter
- Graves ophthalmopathy and pretibial myxedema
- Elevated free T4, low/absent TSH, antibodies to TSH receptors
- Methimazole, carbimazole, and propylthiouracil used medically, with RAI as alternate treatment
- Surgery only for symptomatic or unresponsive patients

MICROSCOPIC


- Entire gland affected, although sometimes unevenly, by diffuse hyperplasia of follicular epithelium

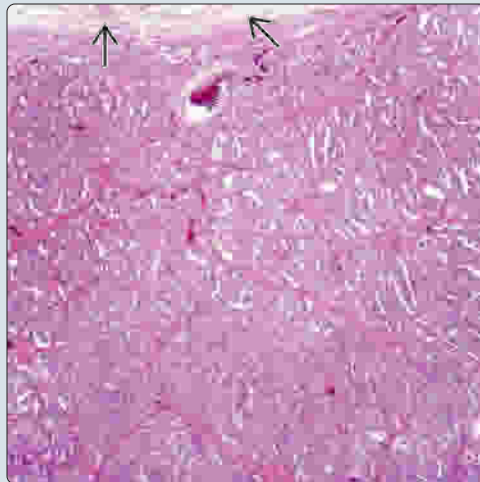
- Follicles show simple, nonbranching papillary projections into lumen
- Colloid is scant (untreated cases), but most cases have been treated, so colloid is seen
- Nuclei are round to oval, regular, basally located with granular to coarse chromatin
- Lymphoid infiltrate, including germinal center formation, is common
- If carcinoma is present, nearly always thyroid papillary carcinoma

TOP DIFFERENTIAL DIAGNOSES

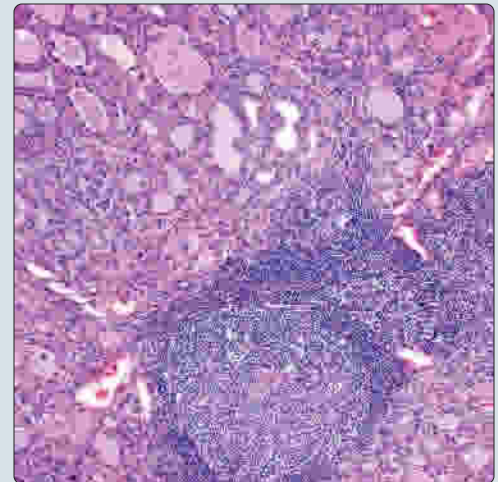
- Thyroid papillary carcinoma
- Chronic lymphocytic thyroiditis
- Toxic nodular hyperplasia
- Dysmorphonogenetic goiter
- Adenomatoid nodules

Diffuse Hyperplasia of All Tissue

(Left) Hematoxylin and eosin shows that all of the tissue in the thyroid gland is affected by the hyperplasia. The thyroid gland edge is noted at the top . There is an accentuation of the fibrovascular septa. Very little colloid is noted. **(Right)** There is a prominent lymphoid follicle in the background. This is frequently seen in patients with Graves disease (GD), as it is an autoimmune disease, mediated by the lymphoid component. This is not interpreted to be chronic lymphocytic thyroiditis (or Hashimoto thyroiditis).

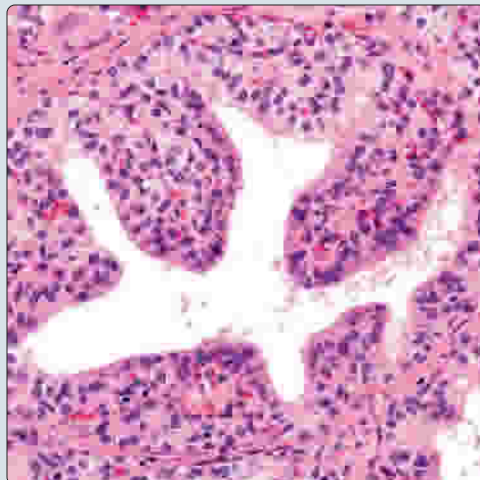


Lymphoid Infiltrate Is Part of Graves Disease

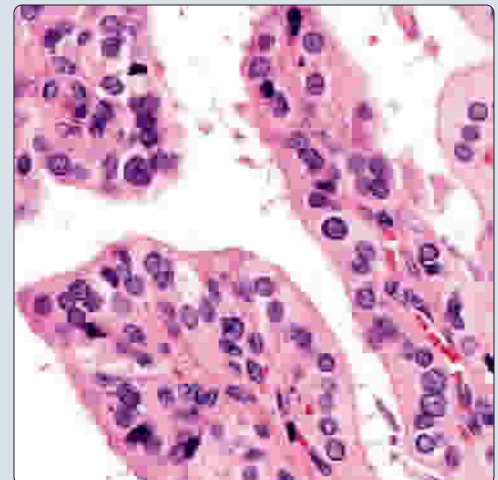


No Colloid in Hyperplastic Follicle

(Left) Hematoxylin and eosin shows blunt, simple papillary projections into a lumen without colloid. This is characteristic for a diffuse hyperplasia. Note the lack of atypia. **(Right)** Hematoxylin and eosin shows a number of simple papillae. Note the tall columnar cell containing a round, regular nucleus with coarse, heavy nuclear chromatin distribution. A delicate fibrovascular core is noted.



Round Nuclei With Coarse Chromatin



TERMINOLOGY

Synonyms

- Diffuse toxic goiter
- Graves disease (GD)

Definitions

- Autoimmune disorder characterized by excessive production of thyroid hormone and diffuse enlargement of thyroid
- Eponymous for Irish physician Robert Graves who described cardiac palpitations, thyroid enlargement, and exophthalmos in 1835

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Iodine supplementation in previously deficient populations is associated with increased risk of hyperthyroidism (Jod-Basedow phenomenon)
 - Unmasks underlying immune modulation abnormality
- Stress
- Smoking associated with increased risk (2-3x) but most significant for ophthalmopathy

Autoimmune

- Genetic susceptibility combined with environmental triggers that precipitate autoimmune response

Female Gender

- Interestingly, there is 6x increase risk of GD post partum
 - May be rebound of immunologic activity after immune tolerance for fetus
 - Fetal cells may accumulate in thyroid (fetal microchimerism), with development of autoimmunity

Genetic

- Concordance rate of 20-35% for monozygotic twins
- *HLA-DR3* associated with increased risk of 3-4x
- Significant association of CD40 C/T-1 polymorphism and GD
- Protein tyrosine phosphatase nonreceptor 22 (*PTPN22*) C1858T gene polymorphism associated with GD (especially in Caucasians)
- *MAGI3* and *BACH2* variants of thyroid peroxidase antibodies (TPOAbs) associated with increased risk of hyperthyroidism
- Polymorphisms of cytotoxic T-lymphocyte antigen 4 gene (*CTLA4*)
- IL1B (-511) polymorphism associated with GD risk in Asians

Pathogenesis

- Hyperthyroidism is due to production of autoantibodies (immunoglobulin: Thyroid stimulating immunoglobulin [TSI])
 - Autoantibodies to extracellular domain of thyroid stimulating hormone receptor (*TSHR*) on follicular cells
 - Previously called long-acting thyroid stimulator (LATS)
 - Sera of patients with GD stimulated thyroids of test animals for longer time than TSH
 - *TSHR* gene is on chromosome 14q31
- Disturbance of balance of immune response and inhibition results in loss of self tolerance, basic feature of autoimmunity

- Autoantibodies activate receptor and stimulate thyroid hormone synthesis and secretion; also cause diffuse proliferation of follicular epithelium
 - There is complex interaction of T and B lymphocytes and thyroid follicular cells with T lymphocytes playing critical role
- Follicular cells may contribute to increased vascularity of thyroid by secreting vascular endothelial growth factor in response to stimulation by TSHR autoantibodies

CLINICAL ISSUES

Epidemiology

- Incidence
 - One of most common autoimmune diseases
 - Prevalence: 0.4-1% (USA population)
 - Annual incidence: 20-25 per 100,000 population
- Age
 - All ages but rare before adolescence
 - Peak incidence: 4th-6th decades
- Sex
 - Female >> male (7-10:1)
- Ethnicity
 - *HLA-B35* is associated with GD among Japanese patients
 - *HLA-Bw46* is associated with GD among Chinese populations

Presentation

- Generalized manifestations of hyperthyroidism
 - Patients present with nervousness, anxiety, fatigue, heat hypersensitivity, increased perspiration, palpitations, increased appetite but with loss of weight
 - Warm moist skin, tremor, tachycardia, hypertension
 - Muscle weakness
 - Personal or family history of autoimmune disease
- Mild to moderate goiter
- Inflammation of orbital tissues (Graves ophthalmopathy)
 - Lid lag and stare
 - Ophthalmopathy is most frequent and significant extrathyroidal manifestation
 - Extraocular muscles become inflamed and edematous
 - Bilateral in 90%, even if symptoms are unilateral
 - Symmetrical in 70%
 - Predilection: Inferior > medial > superior > lateral > oblique ("I'm slow" mnemonic)
 - Orbital fibroadipose tissue and lacrimal glands increase in volume
- Excessive accumulation of glycosaminoglycans in skin
 - Anterior region of leg (pretibial myxedema)

Laboratory Tests

- Elevated free T4
 - Normal free T4 is found in limited number of cases
 - Elevated free T3 instead may prove elevated hormone production
- TSH is abnormally low or undetectable
- Antibodies to TSH receptors are identified in nearly all untreated cases
 - 2 assays
 - TSH binding inhibiting immunoglobulins (TBII): Immunoassay

Graves Disease (Diffuse Hyperplasia)

- TSI: Bioassay
- Assays are not comparable
- TSHR autoantibodies are heterogeneous and can be agonistic, antagonistic, or neutral in their effects on receptor
- Stimulating and blocking antibodies are found
- Alternative names for TBII test include thyroid receptor antibody (TRAb) and long-acting thyroid stimulator (LATS)
- Antibodies to thyroperoxidase (TPO) detected in majority of cases
- Antibodies to thyroglobulin present in ~ 1/2 of patients

Treatment

- Options, risks, complications
 - Low risk of recurrent hyperthyroidism
 - Low to moderate risk of hypothyroidism (post surgery)
 - Higher relapse rates with antithyroid drugs (52.7%) than with RAI (15%)
- Surgical approaches
 - Total or subtotal thyroidectomy (diffuse and bilateral disease)
 - Total thyroidectomy is better than bilateral subtotal thyroidectomy
 - Only used for symptomatic hyperthyroid patients and ineffectively treated or unresponsive patients
 - Also used in children to reduce radiation-induced carcinoma risk
 - Nodule or malignancy is surgical indicator
- Drugs
 - Methimazole, carbimazole, and propylthiouracil are antithyroid drugs
 - Act by primarily inhibiting hormone synthesis through interference with peroxidase-mediated iodination of tyrosine residues
 - Withdrawal of medication may result in relapse of symptoms
 - Nonradioactive iodine inhibits release of thyroid hormones and peripheral conversion of T4 to T3
 - Reduces thyroid vascularity, increases colloid stores, and promotes involution of follicular epithelium
 - Reduction of vascularity helps in presurgical preparation
 - β -adrenergic blockers (propranolol) relieves symptoms (cardiovascular and neurological) but does not affect thyroid gland (per se)
- Radiation
 - RAI is alternate treatment to medical management
 - Patient limitations during treatment may reduce frequency of utilization
 - Ablates thyroid
 - Eliminates signs and symptoms of hyperthyroidism
 - After time, patients will require T4 replacement

Prognosis

- Usually excellent
- Post-treatment hypothyroidism must be managed with replacement therapy

IMAGING

Radiographic Findings

- Diffuse enlargement of entire gland

- Scintigraphic imaging studies with radioiodine reveal diffusely elevated uptake

MACROSCOPIC

General Features

- Diffuse symmetrical enlargement, vaguely nodular
- Variable colors of cut surface depending on vascularity
 - Untreated cases have high vascularity and dark red color
 - Treated cases have decreased vascularity and lighter cut surface
- Spongy to firm
- Resembles skeletal muscle

Size

- 50-150 g

MICROSCOPIC

Histologic Features

- Entire gland is affected, although sometimes unevenly
- Diffuse hyperplasia of follicular epithelium
- Follicles show simple, nonbranching papillary projections into lumen
 - When untreated, papillae are more prominent
- Colloid is scant (untreated cases), but most cases have been treated, so colloid is seen
 - Colloid appears lighter/pale compared to normal thyroids
 - Scalloping is usually prominent, especially at epithelial junction with hyperplastic papillae
- Tall columnar cells with eosinophilic to amphophilic cytoplasm
- Nuclei are round to oval, regular, basally located with granular to coarse chromatin
- Nuclei may be atypical, especially after radioiodine ablative therapy
- Lymphoid infiltrate, including germinal center formation, is common
 - Oncocytic metaplasia adjacent to lymphocytes is not seen
- Fibrosis is limited, although accentuated along septa
 - Heavier in longstanding cases or those treated with RAI
- Extraocular muscles and soft tissue infiltrated by predominantly T lymphocytes
 - Accumulation of excessive amounts of hydrophilic glycosaminoglycans
 - After time, extraocular muscles become atrophic with associated fibrosis

Therapy Effects

- Hyperplastic changes are decreased/regressed but are not uniformly altered
- Hyperplastic areas are still identified
- Colloid is increased
- RAI therapy causes follicular atrophy, fibrosis, oncocytic metaplasia, nuclear atypia, hyperplastic nodules, and persistence of lymphocytic infiltrates

Concurrent Carcinoma

- Nodules can be found, up to 25% of which will contain carcinoma (~ 1-4% overall incidence)
- Nearly all carcinomas are thyroid papillary carcinoma

- Most are incidental/microscopic tumors
- Psammoma bodies may help to focus attention on finding carcinoma

ANCILLARY TESTS

Cytology

- Aspiration is seldom needed, as diagnosis is usually based on clinical findings and laboratory tests
- Scant, bloody material
- Low to moderate cellularity
- Colloid is scant, thin, or pale (especially with Papanicolaou-stained material)
- Follicular cells in flat sheets or microfollicles
- Cytoplasm is increased with pale, finely granular appearance
 - Marginal cytoplasmic vacuolization (clear with Papanicolaou-stained material; pink with Diff-Quik stained material) called flame or flare cells
- Nuclei are slightly enlarged but round with small nucleoli
- Lymphocytes and oncocytic cells can be seen
- Post-treatment aspirates can show atypia

Immunohistochemistry

- TTF-1 and thyroglobulin (+)
- Ki-67 usually < 5%
- p27 in most nuclei
- CD3 and CD20 in appropriate compartments of lymphoid infiltrate

DIFFERENTIAL DIAGNOSIS

Thyroid Papillary Carcinoma

- Not usually diffuse process
- Complex, arborizing or anastomosing papillae
 - Contain fibrovascular cores
- Has distinctive nuclear features of papillary carcinoma (enlargement, folds, grooves, overlapping, chromatin clearing)

Chronic Lymphocytic Thyroiditis

- a.k.a. hashitoxicosis
- Hashitoxicosis exhibits follicular hyperplasia that can mimic GD
- More pronounced oncocytic metaplasia
- Greater lymphocytic infiltrates and germinal centers
- Follicular atrophy and fibrosis also favor lymphocytic thyroiditis

Toxic Nodular Hyperplasia

- Plummer nodule or adenoma
- Must have clinical history and laboratory test results
- Grossly multinodular
- Majority of gland shows follicles with abundant colloid
- Single nodule shows hyperplastic changes, usually encapsulated or very well circumscribed

Dyshormonogenetic Goiter

- Inherited disorder, affecting primarily young patients
 - Familial history usually identified
- All thyroid gland tissue is affected
- Nodules are readily identified

- Remarkably atypical nuclei in follicular epithelium limited to internodular zones
- Colloid tends to be absent or watery

Adenomatoid Nodules

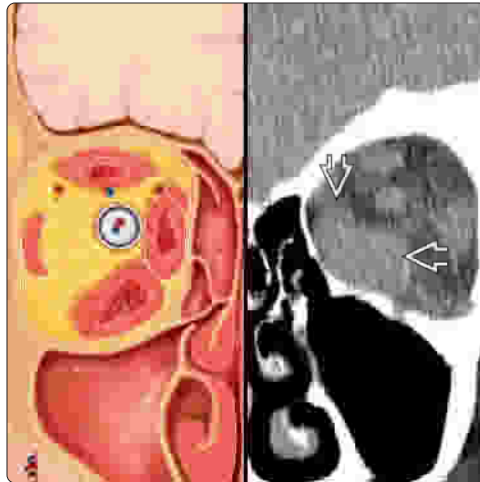
- Multinodular goiter clinically
- Euthyroid usually
- Variably sized nodules but showing normal or uninvolved thyroid parenchyma in background or periphery
- Colloid is usually abundant and easily identified throughout
- Lacks cytologic atypia

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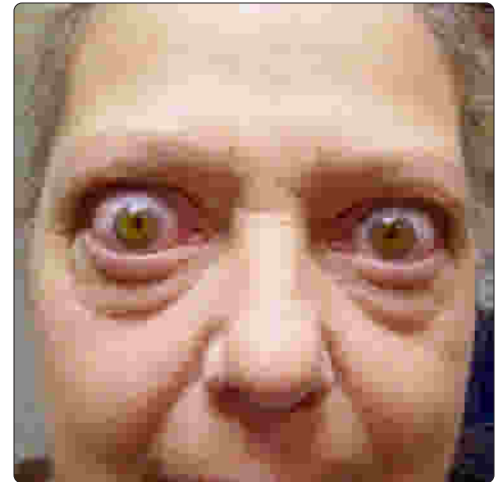
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Graphic and CT of Enlarged Muscles

(Left) A graphic of the enlarged extraocular muscles juxtaposed to a CT demonstrates remarkable infiltration of the extraocular muscles in this patient with GD. (Right) Clinical photograph shows Graves exophthalmos. Note the remarkable proptosis and retraction of the eyelids (lid lag). This is a very characteristic stare of patients with an infiltrative pathology of the extraocular muscles. (Courtesy K.B. Krantz, MD.)

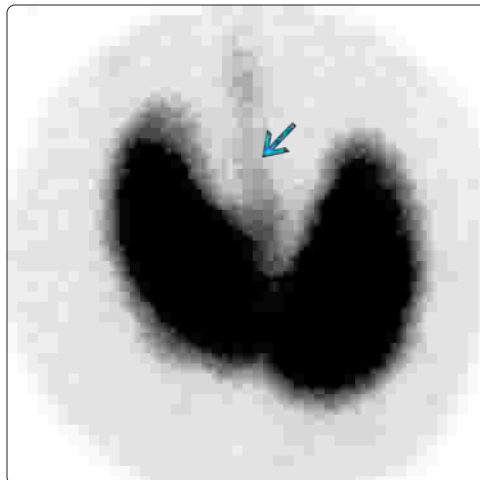


Lid Lag With Proptosis



Enlarged Gland With Diffuse Uptake

(Left) Scintigraphic studies may highlight an enlarged gland. In this case, there is intense uptake in an enlarged thyroid with a prominent pyramidal lobe. It is a frequent finding in GD to see the pyramidal lobe highlighted. (Right) There is a vaguely nodular appearance to this beefy red gland that shows a diffuse symmetrical enlargement. There is a slight change in colloid character.

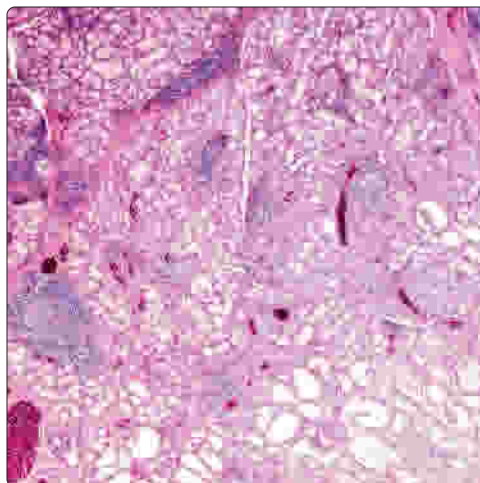


Beefy Red Diffuse Enlargement

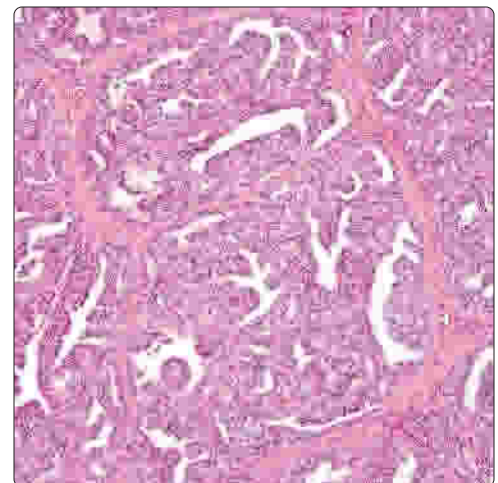


Diffuse Hyperplasia With Limited Colloid

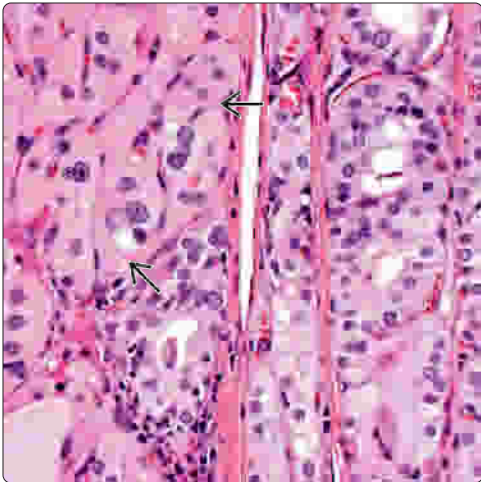
(Left) Hematoxylin and eosin shows a number of lymphoid follicles and collections of lymphocytes in this example of diffuse hyperplasia. The low power can sometimes be confused with chronic lymphocytic thyroiditis. Oncocytic metaplasia is usually limited in GD. (Right) Hematoxylin and eosin shows a noncomplex papillary hyperplasia into the follicle lumen. There is a lack of arborization. The fibrovascular septa separate the nodules. There is no significant colloid in this gland.



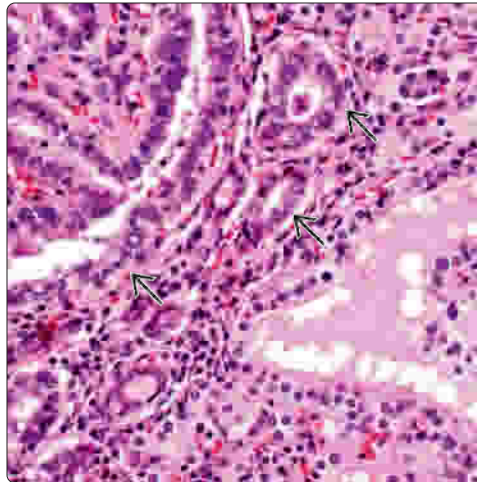
Noncomplex Papillary Hyperplasia



Variability in Cellular Components

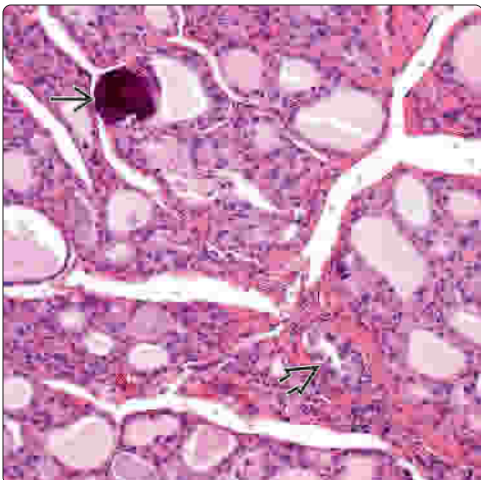


Papillary Carcinoma in Diffuse Hyperplasia

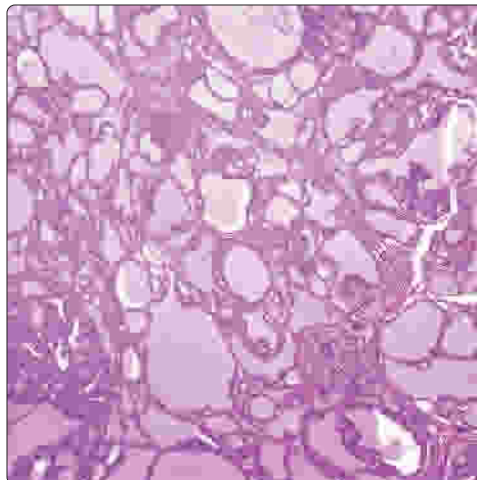


(Left) Hematoxylin and eosin demonstrates the variability that can be seen in diffuse hyperplasia. Granular, oncocyctic (Hürthle) cell changes are present [] and juxtaposed to the right side of the field. (Right) A thyroid papillary carcinoma [] is present in a background of diffuse hyperplasia. There is a sharp difference between the nuclear crowding, nuclear overlapping, increased nuclear size, nuclear chromatin distribution, and optical clearing of the chromatin.

Papillary Carcinoma and Diffuse Hyperplasia

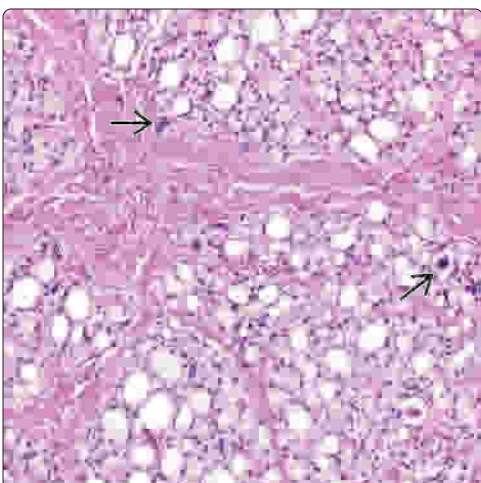


Treatment Effect With Increased Colloid

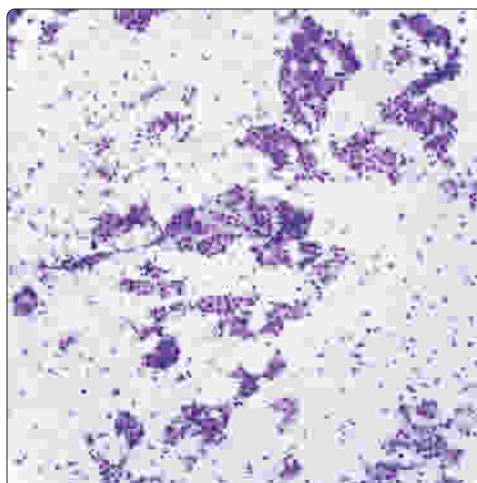


(Left) There is a psammoma body [] in this background of diffuse hyperplasia, while a single island of viable tumor [] is also seen in the same high-power field. Sometimes, the separation between diffuse hyperplasia and papillary carcinoma can be challenging, but size differences and cytologic features can help. (Right) The patient was treated medically, resulting in a remarkable increase in colloid production, although papillary projections into the lumen are still noted, just not as pronounced.

Radiation Treatment of Graves Disease



Cellular Smears in Diffuse Hyperplasia



(Left) There is increased fibrosis between the islands of thyroid follicular epithelium. Isolated atypical nuclei are also present [] but are not specific for radiation treatment. (Right) Diff-Quik demonstrates a cellular smear. There are groups, sheets, and follicles within a background of very thin to nonexistent colloid. Note the abundant flame-type cytoplasm. Overlap with follicular tumors may be seen, requiring clinical separation.

KEY FACTS

TERMINOLOGY

- Fibrosclerosing process of thyroid gland and adjacent soft tissues of neck felt to belong to spectrum of IgG₄-related disease

ETIOLOGY/PATHOGENESIS

- Evidence supports Riedel thyroiditis (RT) being part of spectrum of IgG₄-related diseases based on association with extracervical fibrosclerosing lesions, histologic features, immunohistochemical findings, and response to treatment

CLINICAL ISSUES




- Painless neck mass &/or goiter
- Thyroid is enlarged, woody, or stony hard on palpation and adherent or fixed to surrounding structures
- Presence of hard and fixed thyroid mass clinically simulates neoplastic lesion (i.e., carcinoma)
- Clinically, patients present with stony hard goiter frequently associated with compressive symptoms

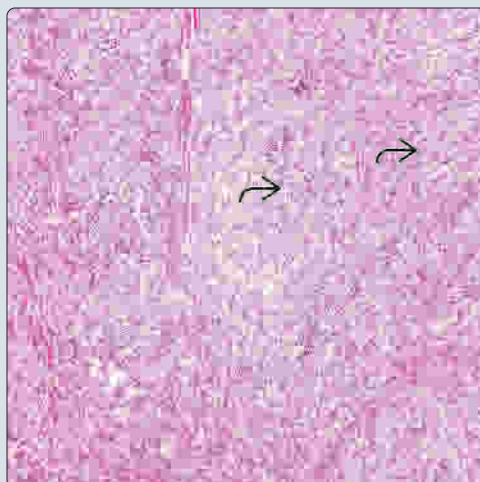
- Hypothyroidism occurs in 30-40% of patients and is permanent; hypoparathyroidism may also occur
- Serum levels of IgG₄ may or may not be elevated
- Wide surgical resection is indicated
- Corticosteroid or rituximab appear to be efficacious treatment (supplanting surgical therapy) associated with clinical and radiologic improvement with

MICROSCOPIC

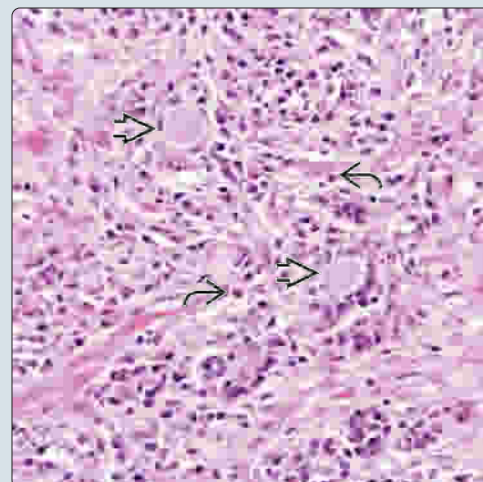
- Destruction and replacement of thyroid parenchyma by dense collagen (keloid-like bands of fibrosis)
- Fibrosing process is not confined to thyroid but also involves extrathyroidal connective tissue structures, such as muscle, adipose tissue, nerves, parathyroid gland(s)
- Inflammatory component predominantly composed of mature plasma cells
- Vasculitis may be present primarily involving veins (phlebitis) may be readily apparent or may be difficult to identify; not present in all cases

Keloid-Like Fibrosis




(Left) Riedel thyroiditis (RT) is characterized by destruction or replacement of virtually all thyroid tissue by dense, keloid-like fibrous bands with an associated chronic inflammatory cell infiltrate. Residual colloid-filled follicles are present  but can be challenging to identify by light microscopy. **(Right)** At higher magnification, there is fibrosis & chronic inflammation composed of mature plasma cells & lymphocytes; scattered eosinophils  are present. Note the residual, colloid-filled follicles  obscured by the inflammatory infiltrate.

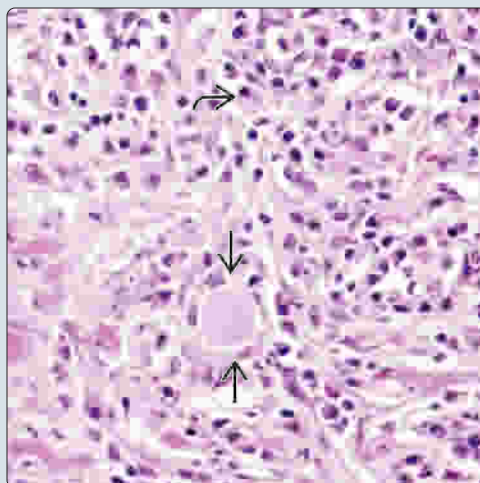


Residual Colloid-Filled Follicles

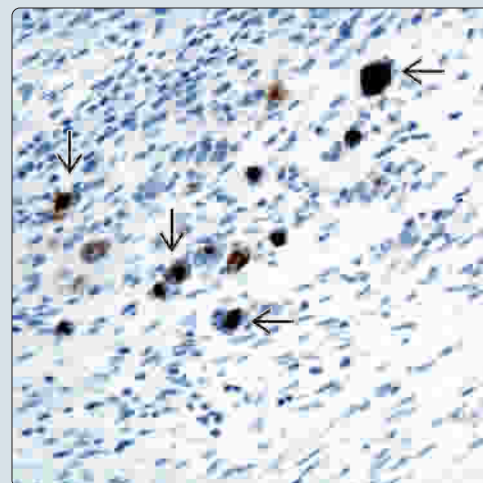


Increase in Mature Plasma Cells

(Left) Numerous mature plasma cells with identifiable Russell bodies  are identified in RT. The plasma cells are characterized by IgG₄(+) staining and increased IgG₄:IgG ratio (not shown) supporting inclusion of RT as an IgG₄-related disease. A residual, colloid-filled follicle is present . **(Right)** Residual thyroid follicular epithelium may be obscured by the fibroinflammatory process and difficult to identify by light microscopy. Thyroglobulin staining is of assistance in highlighting the positive staining follicles .



Thyroglobulin Expression in Follicular Cells



TERMINOLOGY

Abbreviations

- Riedel thyroiditis (RT)

Synonyms

- Invasive fibrous thyroiditis; ligneous thyroiditis

Definitions

- Fibrosclerosing process of thyroid gland and adjacent soft tissues of neck felt to belong to spectrum of IgG₄-related disease

ETIOLOGY/PATHOGENESIS

Systemic Fibrosing Disease/IgG₄-Related Systemic Disease

- Evidence supports RT being part of spectrum of IgG₄-related diseases based on association with extracervical fibrosclerosing lesions, histologic features, immunohistochemical findings, and response to treatment
- Disease process may be localized to thyroid gland and perithyroidal tissues or may be part of systemic fibrosing disease
 - Extracervical fibrosclerosis may include: Retroperitoneum, mediastinum, orbital, pancreas, hepatobiliary, lung, sinonasal tract, salivary glands (parotid, submandibular)
 - Thyroid involvement may coexist with 1 of above sites of involvement

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon disease
- Age
 - Primarily occurs in adults
- Sex
 - Female > male

Presentation

- Painless neck mass &/or goiter
- Pressure in anterior neck often associated with dysphagia, dyspnea, stridor
- Rarely, vocal cord paralysis may occur due to recurrent laryngeal nerve involvement
- Compression and encasement of internal jugular vein and carotid artery may occur
- Thyroid is enlarged, woody, or stony hard on palpation and adherent or fixed to surrounding structures in neck
 - Involvement of thyroid may be limited in extent so that 1 side is predominantly involved
 - Bilateral involvement of thyroid can also occur
- Presence of hard and fixed thyroid mass clinically simulates neoplastic lesion (i.e., carcinoma)
 - Impression of neoplasm further suspected in cases associated with cervical lymph node involvement
- Clinically, patients present with stony hard goiter frequently associated with compressive symptoms
- Involvement of surrounding neck structures, including internal jugular vein, may be progressive, predisposing to cerebral venous sinus thrombosis

Laboratory Tests

- Hypothyroidism occurs in 30-40% of patients and is permanent; hypoparathyroidism may also occur
- Serum levels of IgG₄ may or may not be elevated
- Circulating antithyroid antibodies are usually absent but may be present in lower amounts
 - Presence of antithyroid antibodies may represent reaction to released antigens following follicular epithelial destruction (similar to subacute thyroiditis) rather than representative of an autoimmune condition

Treatment

- Surgical approaches
 - Wide surgical resection is indicated
 - Due to extension of fibrosis from soft tissues of neck into thyroid
 - Uninvolved thyroid need not be resected
- Drugs
 - Corticosteroid or rituximab appear to be efficacious treatment (supplanting surgical therapy) associated with clinical and radiologic improvement with
 - Reduction in lesion size
 - Serologic improvement including progressive decline in serum IgG₄ concentrations
 - ◻ Serum IgG₄ concentrations may remain low and clinical disease activity may remain quiescent in significant proportion of patients

Prognosis

- Favorable symptomatic outcome following surgical resection or following medical management

MACROSCOPIC

General Features

- Replacement of thyroid by dense, tan-white, firm to hard tissue

MICROSCOPIC

Histologic Features

- Destruction and replacement of thyroid parenchyma by dense collagen (keloid-like bands of fibrosis)
- Fibrosing process is not confined to thyroid but also involves extrathyroidal connective tissue structures, such as
 - Muscle, adipose tissue, nerves, and vascular spaces
 - Parathyroid glands can also be involved
- In addition to fibrosis, chronic inflammatory cell infiltrate is present
 - Predominantly composed of mature plasma cells and lymphocytes; eosinophils may be present
 - Giant cells are not present
- Vasculitis is present primarily involving veins (phlebitis) characterized by adventitial inflammation that may invade through full thickness of vessel wall with thrombotic effect
 - May be readily apparent or may be difficult to identify; not present in all cases
- Remnant of thyroid follicles may be present (but may be difficult to identify)
 - Situated within dense collagen
 - Shows atrophic changes

- Not associated with oxyphilic metaplasia (as seen in chronic lymphocytic thyroiditis) or granulomatous inflammation
- In some cases, preexisting or coexisting lesions may be present
 - e.g., adenomatoid nodule(s), follicular adenoma, follicular carcinoma, thyroid papillary carcinoma

ANCILLARY TESTS

Cytology

- Typically, aspiration generates scanty amount of cellular material (dry tap)

Histochemistry

- Elastic stains may be helpful in identifying vasculitis
 - May be helpful in identifying vasculitis
- Periodic acid-Schiff may assist in identifying colloid in thyroid follicles

Immunohistochemistry

- Immunostaining for IgG₄ and IgG show presence of abundant IgG₄(+) plasma cells and increased IgG₄:IgG ratio
- Plasma cells are reactive for CD138, CD79a(+), kappa and lambda light chain staining
- Thyroid follicular epithelium is reactive for thyroglobulin, and TTF-1 can be used to assist in identification of thyroid follicular epithelium

DIFFERENTIAL DIAGNOSIS

Hashimoto Thyroiditis, Fibrosing Variant

- Lacks features associated with RT including
 - Disease process confined to thyroid gland, absence of oxyphilic cytoplasmic change of follicular epithelial cells, absence of phlebitis

Subacute Thyroiditis

- Granulomatous inflammatory condition of thyroid gland
- Histologic findings vary per stage of disease
 - Early phase characterized by destruction of follicular epithelial cells with extravasation and depletion of colloid and colonization of thyroid follicles by inflammatory infiltrate including leukocytes, lymphocytes, histiocytes, and multinucleated giant cells, and microabscess formation
 - Later phase in which leukocytes are replaced by lymphocytes, histiocytes, giant cells, plasma cells; absence of follicular epithelial cells replaced by inflammatory cells
 - Regenerative phase characterized by follicular regeneration with minimal residual irregular fibrosis

Undifferentiated (Anaplastic) Thyroid Carcinoma, Paucicellular Variant

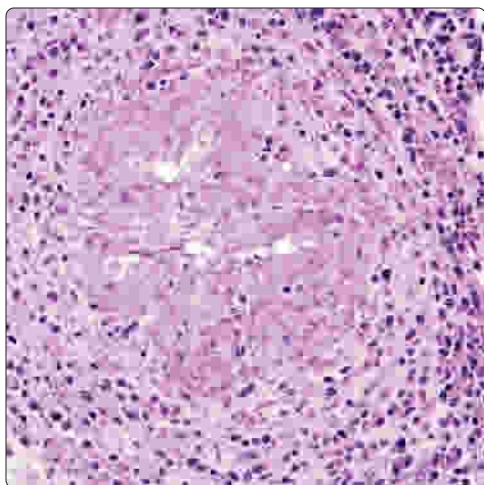
- Uncommon morphologic variant may resemble RT
- Clinical features those of undifferentiated (anaplastic) thyroid carcinoma
 - Occurrence in elderly patients, rapidly enlarging neck mass, rapidly fatal outcome
- Histologic features include
 - Hypocellular foci comprising atypical spindle cells in at least some areas

- Acellular fibrous or infarcted tissue with central dystrophic calcification
- Lymph-vascular invasion
- Lymph node metastasis may be present

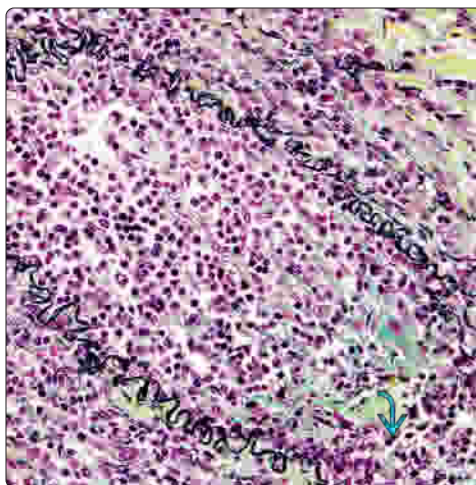
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Phlebitis

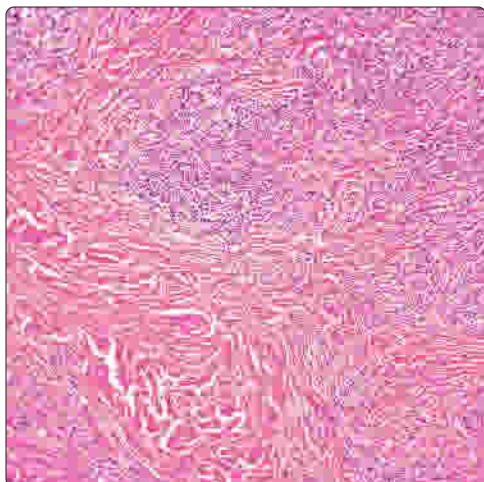


Elastic Membrane Destruction

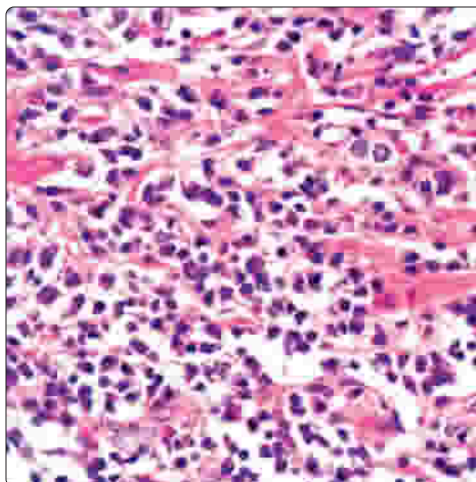


(Left) Vasculitis (phlebitis) is another histologic component seen but may be difficult to identify and is not present in all cases. The inflammatory cells composed of plasma cells and lymphocytes surround (angiocentric) and infiltrate (angioinvasive) an endothelial-lined vascular space. **(Right)** Elastic stain shows focal disruption with discontinuation of the black-staining elastic membrane by the inflammatory cell infiltrate that is present throughout the wall as well as in the lumen (thrombus-like) of vascular spaces.

Keloid-Like Fibrosis

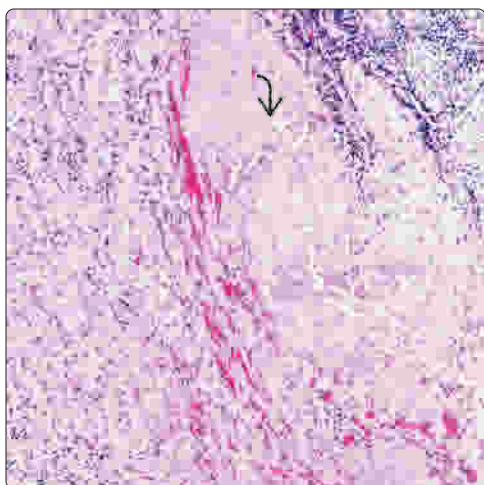


Mature Lymphocytes

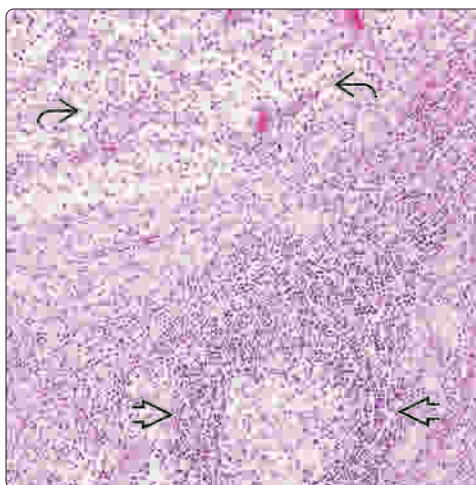


(Left) Keloid-like fibrosis with associated inflammatory cell infiltrate was present in the soft tissues of the neck in a patient with Riedel disease. The clinical presentation included a hard neck mass that was fixed to surrounding structures, including the thyroid gland. **(Right)** At higher magnification, the inflammatory infiltrate seen in association with the extrathyroidal fibrosing lesion includes numerous mature plasma cells as well as mature lymphocytes. There is an absence of thyroid follicles.

Skeletal Muscle Extension



Extension to Parathyroid Gland



(Left) The fibrosing process is not confined to the thyroid but may involve extrathyroidal connective tissue, including skeletal muscle. Other extrathyroidal structures that may be involved include fat, nerves, and vascular spaces (not shown). **(Right)** The disease process may involve the parathyroid gland. The inflammatory cell component may include lymphoid follicles with germinal centers. Parathyroid glands involvement may be associated with clinical and laboratory evidence of hypoparathyroidism.

KEY FACTS

TERMINOLOGY

- Asymmetric, multinodular thyroid gland enlargement due to follicular epithelial hyperplasia as result of impaired thyroid hormone production &/or increased TSH secretion

CLINICAL ISSUES

- Clinically detectable nodules found in < 5% of patients
- Peak: 5th to 7th decades
- Female >> male (5-10:1)
- Thyroid enlargement, often asymmetric and nodular
- Total thyroidectomy for symptomatic disease

IMAGING

- CT is best imaging exam for multinodular goiter

MACROSCOPIC

- Enlarged gland with multiple nodules of variable size
- Cut surfaces are nodular and heterogeneous
- Microscopic to enormous (> 1,000 grams; up to 35 cm)

MICROSCOPIC

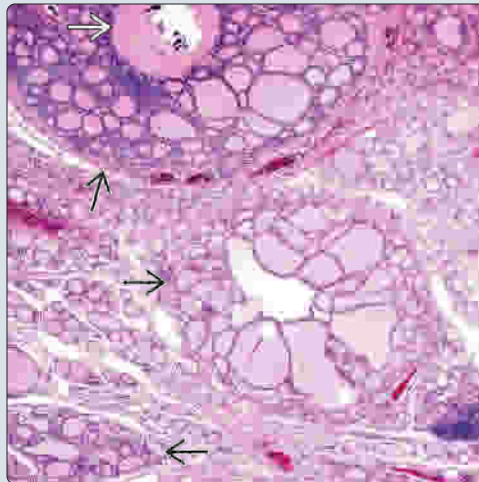
- Nodules lack capsule, showing pushing border that merges with surrounding follicles
- Pseudocapsule of fibrosis lacks elastic fibers and smooth muscle-walled vessels
- Large follicles distended with colloid, often with papillae
- Papillae are simple, lacking complexity and arborization
- Flattened, cuboidal, columnar to oncocytic cells
 - Granules of hemosiderin are frequently present in cytoplasm
- Secondary and metaplastic changes are common
- FNA does not reliably separate nodules from neoplasia

TOP DIFFERENTIAL DIAGNOSES

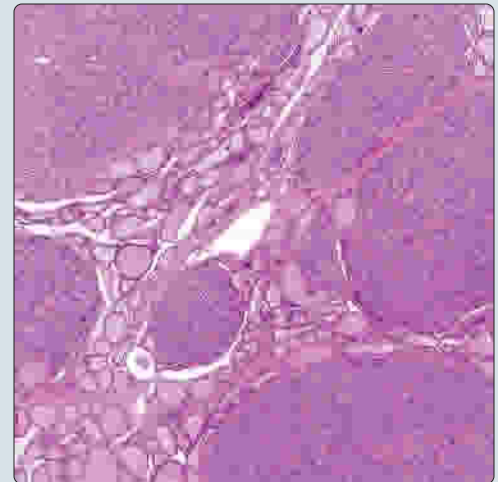
- Follicular adenoma, papillary carcinoma, follicular carcinoma
- Dyshormonogenetic goiter, metastatic carcinoma, amyloid goiter

Multiple Adenomatoid Nodules

(Left) There are multiple adenomatoid nodules in this section. There is a fibrous connective tissue surrounding one of the nodules, while focal degeneration is noted. (Right) Low power shows multiple nodules separated by unremarkable thyroid parenchyma. The nodules show increased cellularity but lack a fibrous connective tissue capsule.

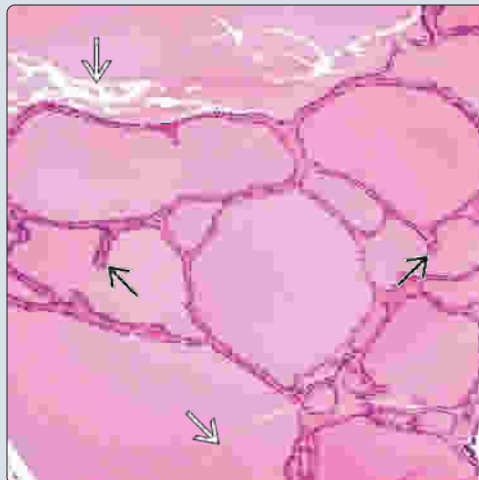


Cellular Adenomatoid Nodules

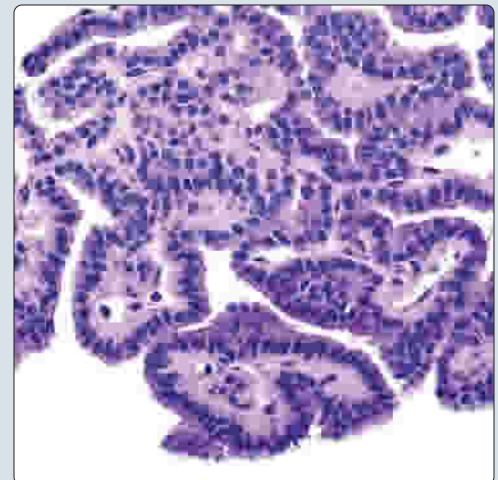


Large Dilated Follicles

(Left) This nodule contains large follicles distended with abundant colloid. There are a number of simple papillary projections into the colloid. Note the cracking artifact in the colloid. (Right) There are several simple papillae in this adenomatoid nodule. There are no complexity and no true fibro-vascular cores in the papillae.



Simple Papillae in Adenomatoid Nodule



TERMINOLOGY

Synonyms

- Multinodular goiter [MNG (clinical term)]
- Adenomatous hyperplasia
- Nontoxic nodular goiter
- Colloid goiter

Definitions

- Asymmetric, multinodular thyroid gland enlargement due to follicular epithelial hyperplasia as result of impaired thyroid hormone production &/or increased TSH secretion
 - "Goiter" is a nonspecific clinical term meaning thyroid enlargement; it is not a surgical pathology diagnosis

ETIOLOGY/PATHOGENESIS

Etiology

- Multifactorial: Intrinsic thyroid follicular epithelial cell alterations with environmental and genetic factors
- Deficiency of dietary iodine
 - Amplified by tobacco use (smoking), probably thiocyanate
 - Low iodine concentration within nodules probably secondary rather than primary
 - Many facets of adenomatoid nodules are not explained by iodine deficiency
 - Many times, goiter size is inversely proportional to serum TSH
- Due to consumption of high volumes of goitrogenic foods
 - Generally raw (cooking inactivates goitrogens)
 - **Cruciferous** vegetables (genus *Brassica*; family *Brassicaceae*)
- Medications, specifically those which may interfere with thyroid hormone synthesis &/or release
 - Iodine, amiodarone, lithium, thioamides (methimazole, carbimazole, propylthiouracil), thalidomide, perchlorate, rifampin, carbamazepine
- Inherited
 - Dyshormonogenetic goiter
 - Increased incidence in monozygotic compared with dizygotic twins

Pathogenesis

- Pathway of nodule production
 - Impaired thyroid hormone production: iodine deficiency, goitrogens, medication blockage (organification of iodine is disrupted)
 - Increases secretion of TSH
 - Many paracrine and autocrine factors are also involved
 - Stimulates thyroid follicular epithelium to proliferate; remarkable functional and structural heterogeneity in thyrocytes results in profound variability
 - Results in increased thyroglobulin production
- Results in formation of adenomatoid nodule (elemental unit)
- Multiple adenomatoid nodules result in clinical goiter (aggregated units)
 - Become autonomous, TSH-independent growth

CLINICAL ISSUES

Epidemiology

- Incidence
 - Clinically detectable nodules found in < 5% of patients
 - Higher in autopsy series, especially if microscopic nodules included (up to 50%)
 - Highest incidence in areas with iodine-deficient diets; may also occur with excess iodine intake
- Age
 - Wide age range, although usually adults
 - Peak: 5th to 7th decades
- Sex
 - Female > > male (5-10:1)
 - Nodules frequently detected during pregnancy

Presentation

- Thyroid enlargement, often asymmetric and nodular
- May be detected during routine physical exam
- Infrequently, stridor (tracheal compression), hoarseness (recurrent laryngeal nerve impingement), or dysphagia (interference with swallowing) may be present
- If there is mediastinal goiter, superior vena cava syndrome may be present
- Signs and symptoms usually develop gradually
 - Rapid enlargement may result from intralesional hemorrhage
- Single or dominant nodule may suggest neoplasm

Laboratory Tests

- Most patients are euthyroid
 - Few patients are hyperthyroid (toxic nodular goiter or Plummer disease)
- Usually normal: TSH and free T4 levels
- Low TSH level: Normal free T4 and free T3

Treatment

- Options, risks, complications
 - Potential complications after thyroidectomy
 - Permanent hypoparathyroidism (up to 7%)
 - Transient or permanent recurrent laryngeal nerve palsy (up to 1.5%)
 - Hypothyroidism may develop, requiring lifelong replacement therapy
- Surgical approaches
 - Total thyroidectomy for symptomatic disease
 - Patients with lobectomy frequently require later completion thyroidectomy for recurrent disease
 - Used for dominant nodule, suspicious for neoplasm
 - Histologic examination helps to exclude unexpected malignancies (detected in up to 7-10% of cases)
- Drugs
 - TSH suppression therapy: Thyroxin suppresses nodules but best for small goiters
- Radiation
 - I-131 therapy
 - Especially in elderly patients, patients with toxic nodules, or patients unwilling to have surgery
 - When surgery is contraindicated or in poor surgical candidates
 - Reduces nodules, but changes are slow

Prognosis

- Multinodular goiters are usually treated for cosmetic or comfort reasons
 - Surgery achieves immediate and permanent cure without recurrence
- Watchful waiting if there are no changes in signs or symptoms
- No risk of malignant transformation
 - However, incidental or concurrent malignancies may be present

IMAGING

Radiographic Findings

- Diffusely enlarged thyroid with multiple nodules
 - Often show substernal extension (~ 1/3)
- CT or US helps assess multinodular goiter
 - Identifies extent and severity of airway compression
 - Presence and extent of substernal goiter

Ultrasonographic Findings

- Hypoechoic solid nodules, anechoic cysts, hyperechoic fibrotic/hemorrhagic regions
- Used to guide FNA procedure

CT Findings

- Inhomogeneous enhancement in enlarged thyroid with multiple cystic and solid masses
- Circumscribed regions of low attenuation (colloid cysts) although high attenuation with hemorrhage
- Calcifications frequently noted

Nuclear Medicine

- Heterogeneous radiotracer uptake with irregular, nodular thyroid contour
- Discrete nodules may be hot (increased activity), cold (photopenic), warm, or isointense (not visualized)

MACROSCOPIC

General Features

- Enlarged gland with multiple nodules of variable size
 - Asymmetric, single, dominant nodule may be seen
 - Thyroid contour distorted
- Cut surfaces are nodular and heterogeneous
 - Gelatinous with colloid exuding from cut surface
 - Glistening and semitranslucent
 - Fleishy to beefy to firm
 - Degenerative/secondary changes
 - Hemorrhage, central scars, fibrous pseudocapsules, cystic change, calcification, and metaplastic bone formation
- Parasitic nodules attached by thin, delicate fibrous strands adjacent to main thyroid gland
 - Attachment may be missed intraoperatively
 - Lack lymph node architecture (subcapsular sinus, sinus histiocytosis, medullary zone) but may show lymphoid infiltrate

Sections to Be Submitted

- Sample periphery of nodules or different nodules (to exclude malignancy)

Size

- Microscopic to enormous (> 1,000 grams; up to 35 cm)

MICROSCOPIC

Histologic Features

- Remarkable nodularity of the examined tissue
 - While uncommon, compression of surrounding parenchyma may be present
- Nodules lack capsule, showing pushing border that merges with surrounding follicles
 - Pseudocapsule of fibrosis lacks elastic fibers and smooth muscle-walled vessels
 - Fibrosis may be circumferential but tends to be irregular and incomplete
 - Areas of increased cellularity throughout parenchyma
- Most nodules contain large follicles distended with colloid
 - Follicles may be small to massively distended with lakes of colloid
 - Papillary projections may be prominent
 - Papillae are simple, lacking complexity and arborization
 - Contain round, basally oriented nuclei with coarse, dense chromatin
 - Polarity of cells is maintained
 - Clusters of follicles (Sanderson polsters) may expand into colloid
- Some nodules may be dominant or cellular with increased cellularity (solid, microfollicular) and little colloid
- Lining epithelium
 - Flattened and inconspicuous epithelial cells
 - Cuboidal or columnar epithelial cells
 - Granules of hemosiderin are frequently present in cytoplasm
 - Prominent oxyphilic change
 - Oncocytic cells may have nuclear enlargement, vesicular chromatin, irregular nuclear contours, and prominent nucleoli
 - Clear cell or signet ring vacuoles
- Secondary changes are common
 - Hemorrhage common, with hemosiderin-laden macrophages
 - Organization shows endothelial hyperplasia (similar to intravascular papillary endothelial hyperplasia)
 - Cystic change with multiple histiocytes in background
 - Cholesterol clefts
 - Fibrosis, often in center of nodule
 - Granulation tissue reaction
 - Dystrophic calcifications
 - FNA site (abrupt, linear disruption) is frequently seen
- Metaplastic change can be seen
 - Osseous metaplasia, especially near dystrophic calcification
 - Cartilaginous metaplasia less common
 - Squamous metaplasia
 - Adipose metaplasia
- Chronic, acute, &/or granulomatous inflammation (due to follicle rupture) may be seen
- Concurrent, topographically distinct neoplasms may be present
 - Microscopic papillary carcinoma is most common

ANCILLARY TESTS

Cytology

- Aspirate may be scant to abundant, thin to viscous, and serosanguineous to red or brown
- Usually low cellularity and abundant, thin colloid
 - Colloid yields proteinaceous film that has scratches, waves, cracks, or mosaic-like artifacts after drying
- Large, flat sheets of follicular epithelium arranged in honeycomb pattern
 - Monolayer sheets of evenly spaced cells
 - Microfollicular groups &/or isolated cells
 - Oncocytic cells may be present (dominant finding or isolated)
- Nuclei are small, round, with dense chromatin
 - No overlapping, crowding or contour irregularities
- Background of hemosiderin-laden macrophages or foamy histiocytes when degenerated
- Multinucleated giant cells may be seen
- Difficult to reliably predict nodules from neoplasia
 - Abundant colloid favors adenomatoid nodule
 - High cellularity with scant colloid favors neoplasm
 - Application of molecular techniques (*BRAF* specifically) may help separate suspicious nodule from papillary carcinoma in selected FNA samples

Frozen Sections

- Seldom of value in nodular process
 - In most cases, "deferred, follicular lesion" does not change management
 - Follicular neoplasm requires complete capsule evaluation for capsular or vascular invasion, task impractical during constraints of intraoperative analysis
- If FNA was indeterminate, intraoperative assessment is often indeterminate too
 - Touch preparations/smears can confirm papillary carcinoma
 - Selection of single nodule for frozen section, only in rare instances of high clinical suspicion of malignancy

Genetic Testing

- Some susceptibility genes related to development of nodules include
 - Thyroglobulin, thyroperoxidase, sodium iodide symporter, and thyroid-stimulating hormone receptor (*TSHR*)
 - Loci include *DICER1* (*MNG1*) and *TSHR* on chromosome 14q
- Occasionally, numerical &/or structural abnormalities are detected
 - Trisomy or tetrasomy 7 is most common

DIFFERENTIAL DIAGNOSIS

Follicular Adenoma

- Single nodule, surrounded by variably thick fibrous connective tissue capsule with smooth muscle-walled vessels
- Usually has single histologic pattern, compressing adjacent thyroid parenchyma, limited colloid
- Tends to lack degeneration and lacks colloid lakes

- Both lesions may be present, but, philosophically, multiple follicular nodules without invasion are within adenomatoid nodule category

Papillary Carcinoma

- Architecture of papillary carcinoma may overlap adenomatoid nodules
- Nuclear features of papillary are required
- In single nodule, if there are multiple topographically separate and distinct areas, especially at periphery, showing nuclear features of papillary, whole tumor should be called papillary carcinoma (especially with follicular variant)
- In borderline case, panel of galectin-3, *MSG1* (*CITED-1*), and *HBME-1* or molecular analysis (*BRAF* mutation specifically) may help with separation

Follicular Carcinoma

- Encapsulated neoplasm with variably thick capsule, showing capsular &/or vascular invasion
- Molecular evaluation (*PAX8/PPARG* [*γ*]) may be of value in some cases

Dyshormonogenetic Goiter

- Grossly similar although colloid is usually limited to absent
- Multiple nodules histologically, but isolated pleomorphic nuclei present in internodular zones

Metastatic Carcinoma

- Parasitic adenomatoid nodules may cause confusion with metastatic papillary carcinoma
- Lymph node architecture must be identified
- Nuclear features of papillary carcinoma can usually be identified

Amyloid Goiter

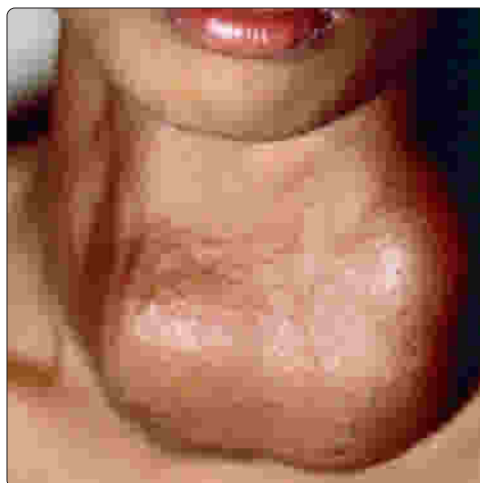
- Demonstrates elongated vessels, squamous metaplasia, fatty metaplasia and perivascular amyloid deposition
- Nodules seen in both lesions

SELECTED REFERENCES

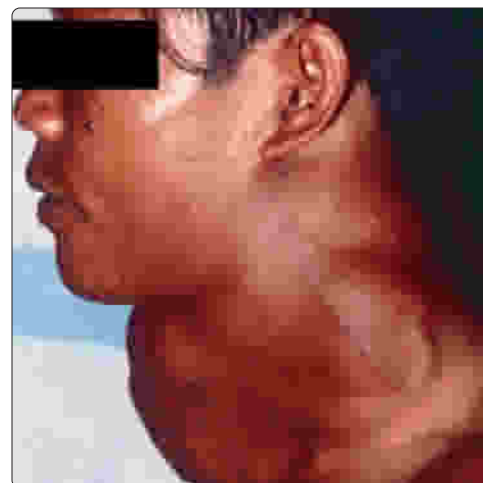
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Goiter Affecting a Patient With Nodules

(Left) The gross photograph demonstrates a large thyroid gland, with multiple nodules within both lobes. This is a characteristic finding in adenomatoid nodules. **(Right)** This patient shows a greatly enlarged thyroid gland (goiter) that at surgery showed multiple adenomatoid nodules. Goiter is a clinical term, while adenomatoid nodules is a histologic diagnostic term.

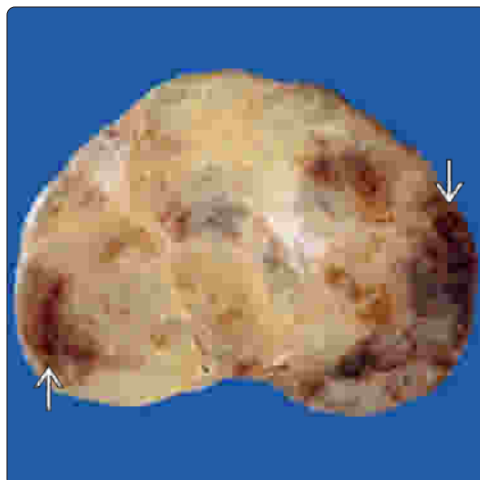


Greatly Enlarged Thyroid Gland

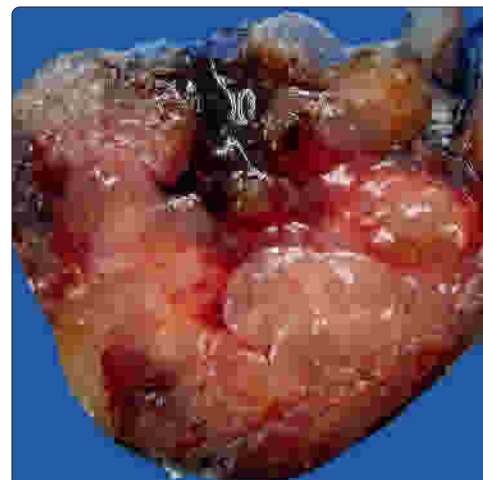


Multiple Nodules in Thyroid Gland

(Left) This gross sample demonstrates multiple nodules, separated by very thin and delicate fibrous bands. There are hemorrhage and areas of degeneration in these nodules. **(Right)** This gross photograph shows multiple adenomatoid nodules within the thyroid gland. There is hemorrhage in some of the nodules. Note the glistening and slightly cleared appearance.



Multiple Adenomatoid Nodules

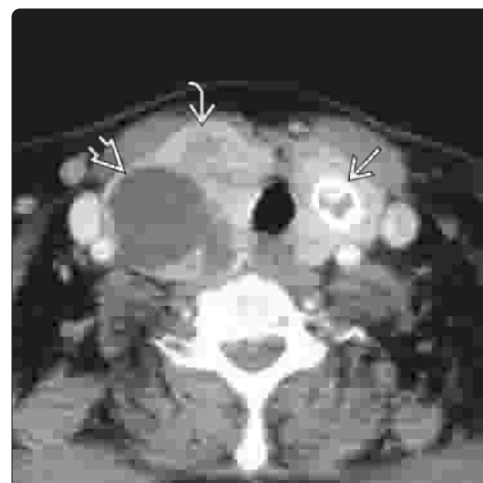


Ultrasound of Multiple Thyroid Nodules

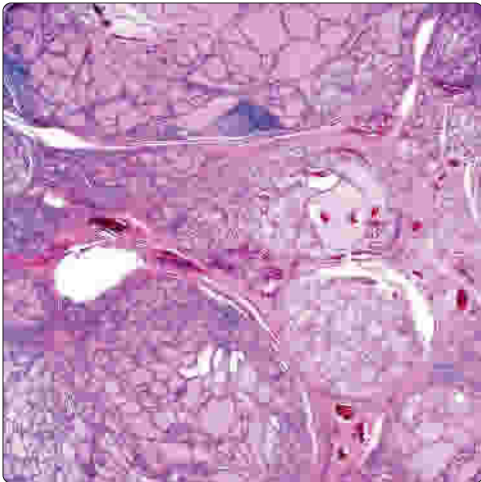
(Left) Transverse grayscale ultrasound shows septations in a well-defined, cystic thyroid nodule in multinodular goiter (MNG). Such nodules are commonly seen in MNG. **(Right)** There is a remarkably enlarged thyroid gland, showing multiple different nodules in this CT scan. The thyroid shows areas of calcification, cystic degeneration, and a more solid area. These changes are characteristic of adenomatoid nodules.



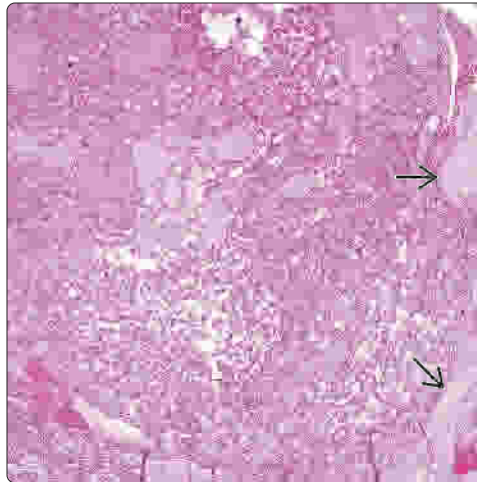
CT: Calcifications in Adenomatoid Nodules



Multiple Nodules

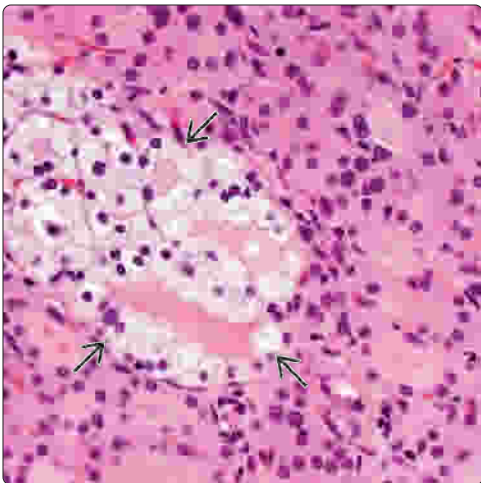


Fibrosis at Nodule Periphery

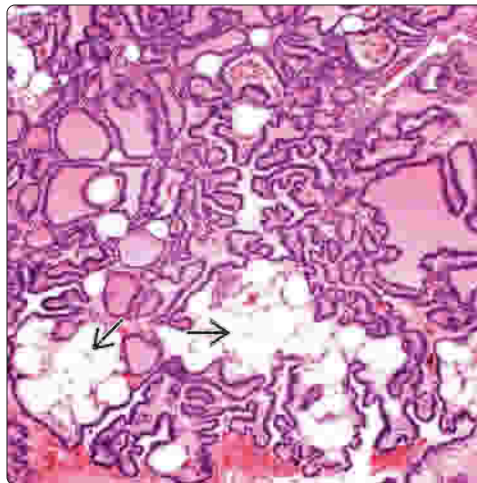


(Left) Incomplete fibrosis is associated with the nodules. Note the multinodular appearance, with the nodules showing variable cellularity and circumscription. Colloid is easily identified in these nodules. **(Right)** The periphery of the nodule shows fibrous connective tissue condensation. The nodule shows variable cellularity, with some areas containing more colloid than others. Areas of edematous change are also present.

Histiocytes in Adenomatoid Nodules

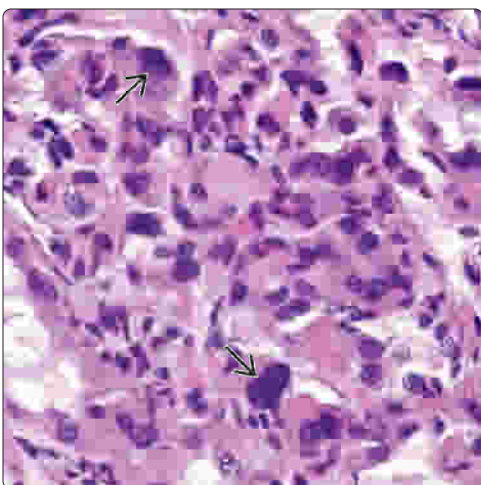


Fatty Metaplasia in a Nodule

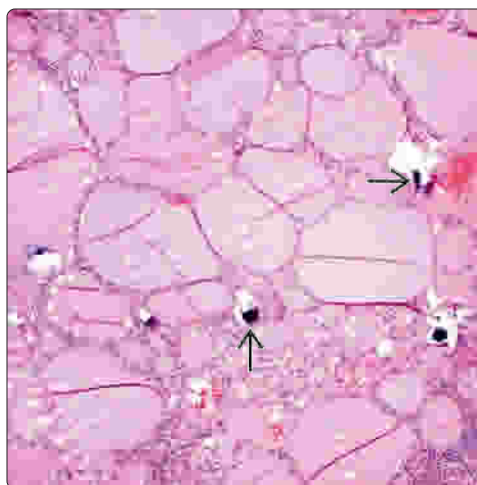


(Left) A variety of cellular features can be seen in nodules. Here is a single focus of clear cell change in a nodule that shows more of an oncocyctic or oxyphilic cytoplasm in the lesional cells. Alterations like this are common. **(Right)** Colloid is easily identified in this nodule, with simple, nonarborizing papillae extending into the colloid-filled spaces. Fatty metaplasia is noted throughout this nodule.

Isolated Pleomorphic Cells



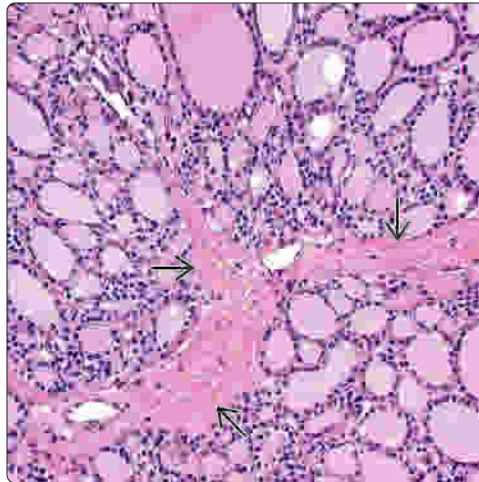
Calcifications Within Colloid



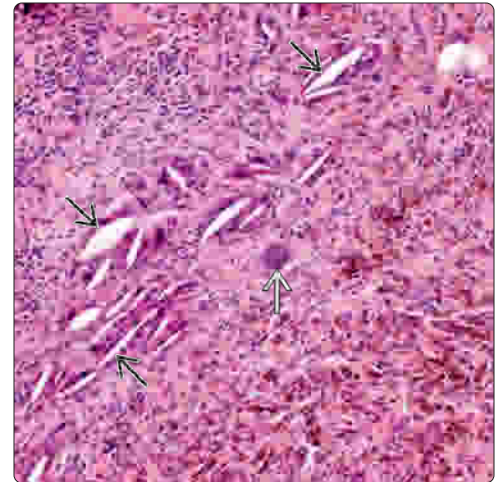
(Left) Rare, isolated cells may show nuclear pleomorphism. This isolated finding is of no clinical significance, but it is common in endocrine organ lesions. This finding is frequently present in adenomatoid nodules. **(Right)** Adenomatoid nodules will frequently show degenerative changes, which includes cyst formation, hemorrhage, and calcification. In this case, the calcifications appear as psammomatoid bodies.

(Left) This nodule demonstrates an area of central fibrosis [box]. Fibrosis is frequently identified in nodules as part of a degenerative or secondary change. It is often seen in the post-FNA setting as well as in association with hemosiderin-laden macrophages. **(Right)** Cholesterol clefts [box], a multinucleated giant cell [box], and sheets of hemosiderin-laden macrophages are frequently identified degenerative changes within adenomatoid nodules.

Fibrosis Within a Nodule

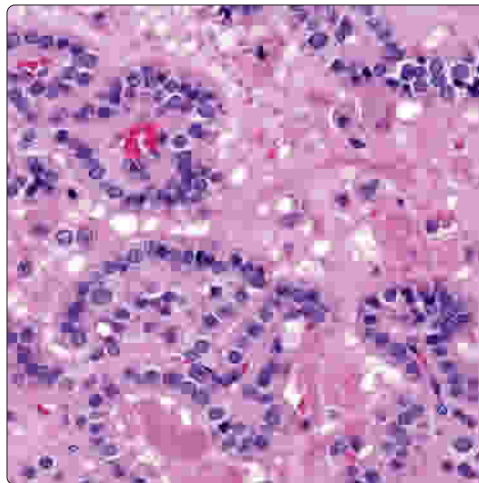


Cholesterol Clefts and Hemosiderin

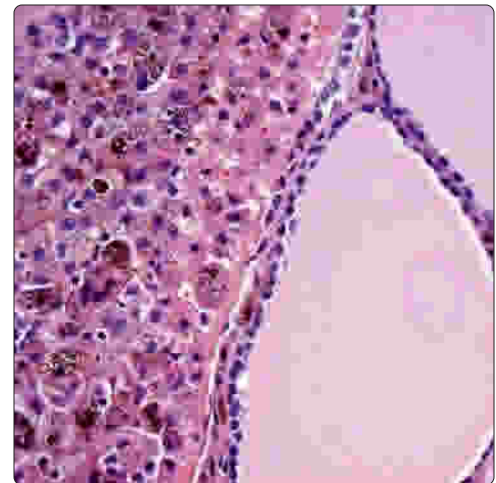


(Left) Hemosiderin-laden macrophages are present in the colloid of this nodule. Most of the follicular epithelial cells contain hemosiderin pigment within their cytoplasm, a finding frequently seen in this benign condition. This feature is vanishingly rare in neoplasms. **(Right)** The histiocytes in this field are filled with hemosiderin. It is not uncommon in nodules to have hemorrhage, which results in associated histiocytes with hemosiderin.

Hemosiderin-Laden Macrophages

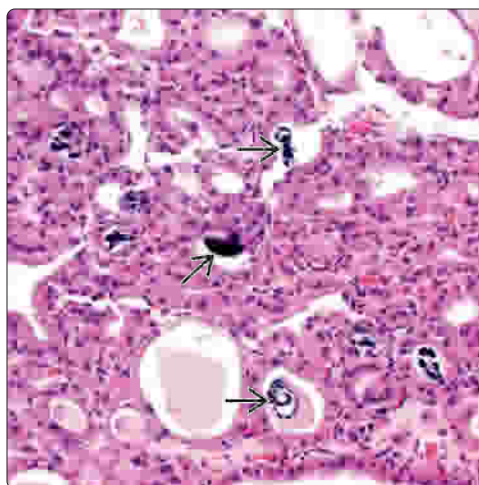


Sheets of Histiocytes

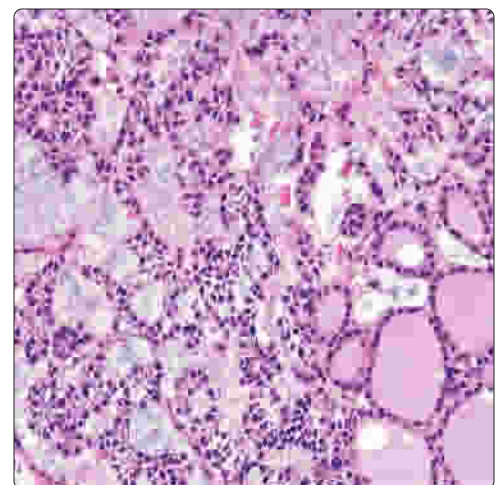


(Left) Dystrophic calcifications are often large "chunks" of calcium, but they may also be small concretions of calcium within the colloid spaces [box]. These mimic psammoma bodies and are seen more frequently in oncocytic nodules than other types of nodules. **(Right)** Nodules will frequently show degenerative changes, and myxoid or edematous change is one of the most commonly seen. Here a "myxo-mucinous" change is seen within the background stroma of this nodule.

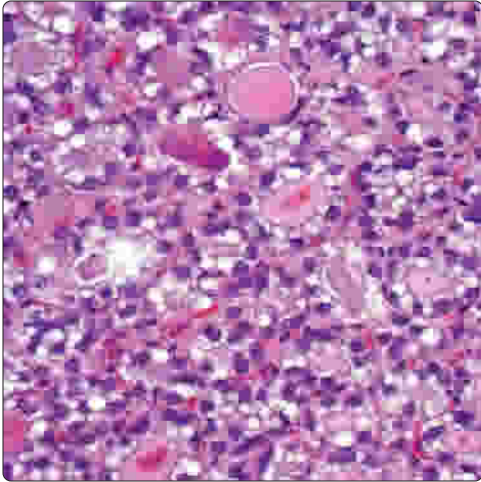
Follicular Calcifications



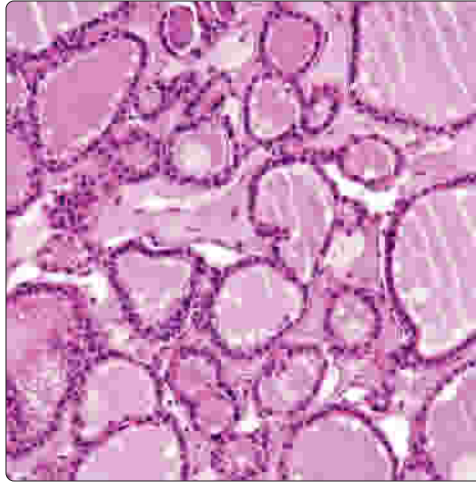
Myxoid Degeneration in Nodules



Cleared to Signet-Ring Changes

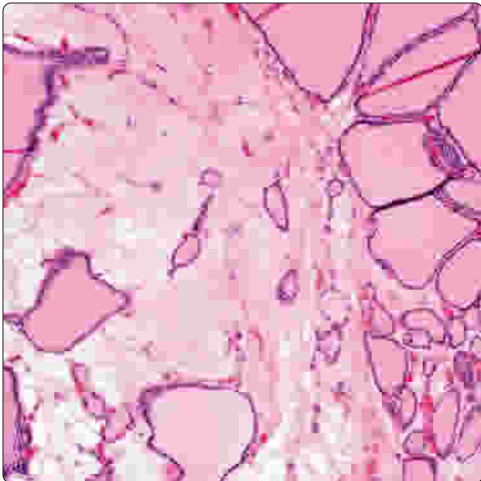


Ample Colloid Within Follicles

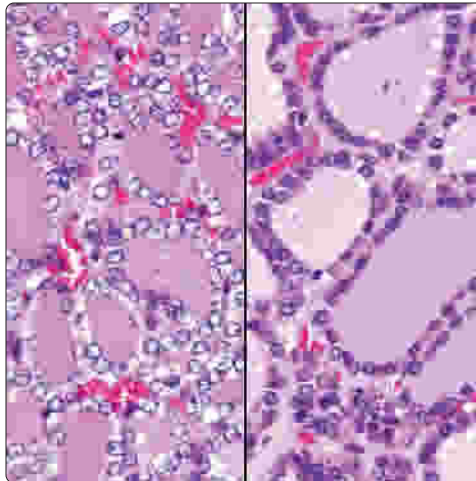


(Left) Nodules may show a variety of different cellular appearances, as seen in this example of cells with cleared to signet-ring changes. These spaces represent abnormal thyroglobulin. **(Right)** Most nodules have abundant colloid within the expanded follicles. The follicular epithelium is low cuboidal, with dark, hyperchromatic nuclei basally polarized.

Edema in Adenomatoid Nodules

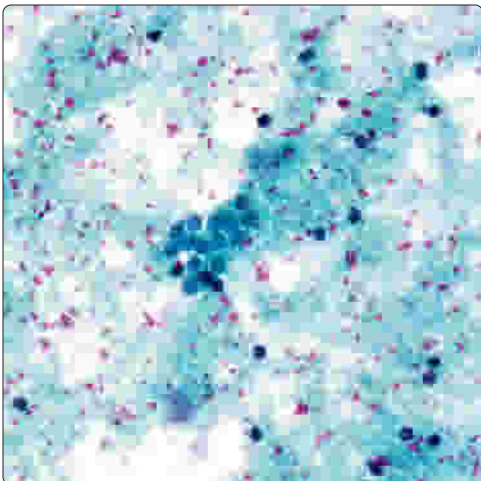


Fixation Changes in Nodules

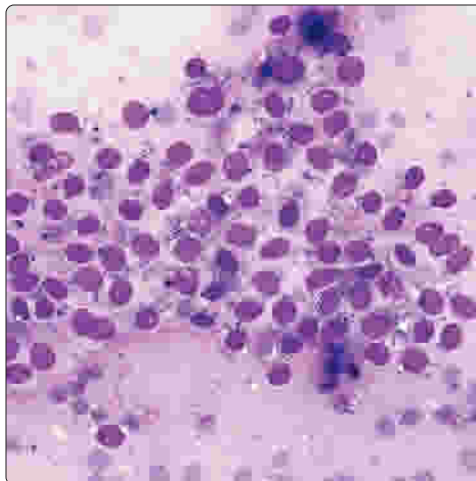


(Left) Edema or serum is present within this nodule, creating a large space. The colloid-filled follicles have a different appearance than the area of degeneration. **(Right)** Fixation artifacts are common in nodules. (L) Nodule was stained after drying on a heating block for 4 hours with excess water in the clearing solution. (R) The exact same nodule was air dried without excess water. Optimal processing of nodules is critical for accurate diagnosis.

Degenerated Colloid and Histiocytes



Hemosiderin in Follicular Epithelium



(Left) Adequacy criteria for thyroid FNA require at least 6 groups/clusters of benign follicular cells, each group composed of at least 10 cells, per slide. Here is a single cluster of 15 cells in a background of degenerated colloid and histiocytes. **(Right)** A large, flat sheet of follicular epithelial cells arranged in a honeycomb is quite frequently seen in adenomatoid nodules. Note the slightly "bluish" granularity of the hemosiderin pigment in the cytoplasm of these cells. This feature is more common in benign than malignant lesions.

Amyloid Goiter

KEY FACTS

TERMINOLOGY

- Symptomatic mass or clinically detectable thyroid enlargement due to amyloid deposition

ETIOLOGY/PATHOGENESIS

- Most common setting of amyloid in thyroid is in association with medullary thyroid carcinoma
- Amyloid deposition in thyroid can occur as part of both primary and secondary systemic amyloidosis
- More commonly seen as part of secondary systemic amyloidosis
 - In this setting, amyloid is usually found at autopsy rather than resulting in symptomatic mass

CLINICAL ISSUES

- In symptomatic amyloid goiter, clinical presentation includes
 - Nontender enlarging neck mass that may be associated with dysphagia, dyspnea, and hoarseness

- Patients are euthyroid
 - Thyroid dysfunction not generally present
- In association with medullary thyroid carcinoma serum calcitonin levels are elevated

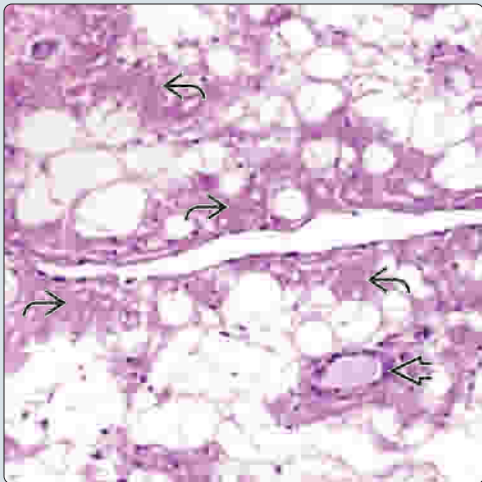
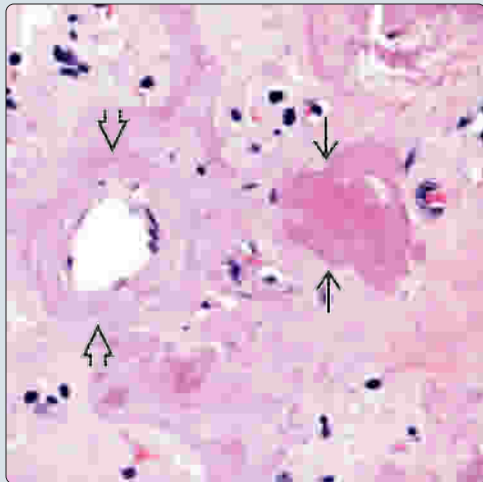
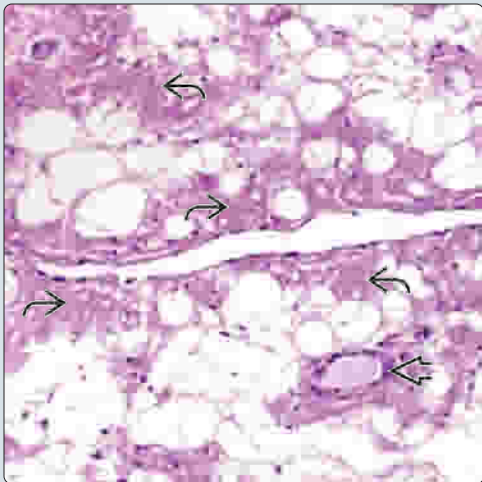
MICROSCOPIC

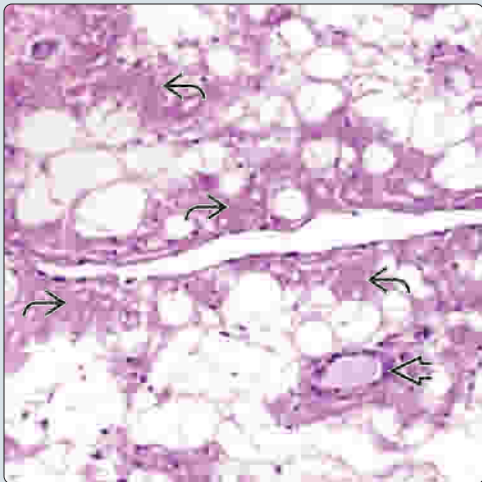
- Diffuse amyloid deposition usually seen, but focal (nodular) deposits may occur
- Amyloid appears as extracellular eosinophilic, acellular, amorphous material
- Amyloid seen in both perifollicular and interfollicular locations compressing follicles
- Amyloid deposition seen around vascular spaces ("angiocentric")

ANCILLARY TESTS

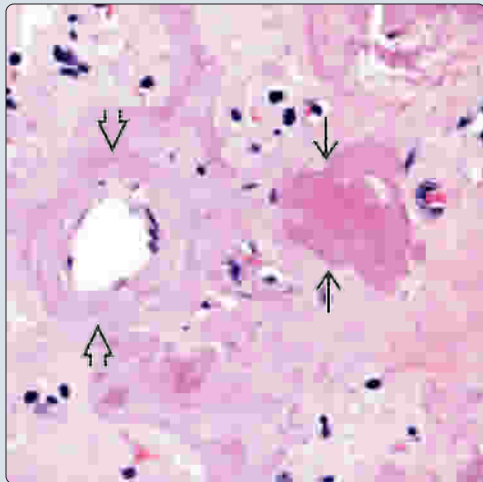
- Congo red, crystal violet, thioflavin-T positive
- Positive immunoreactivity with amyloid A (AA) antibody

Amyloid and Fat

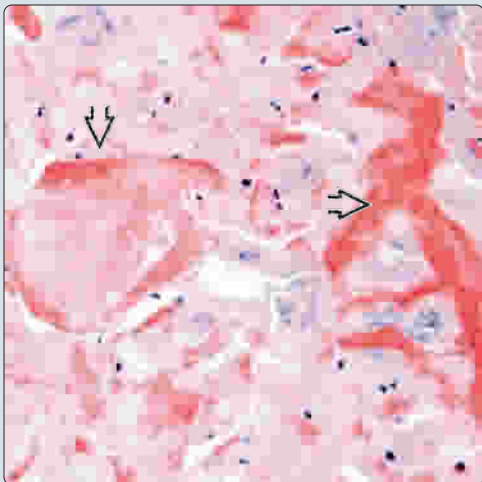
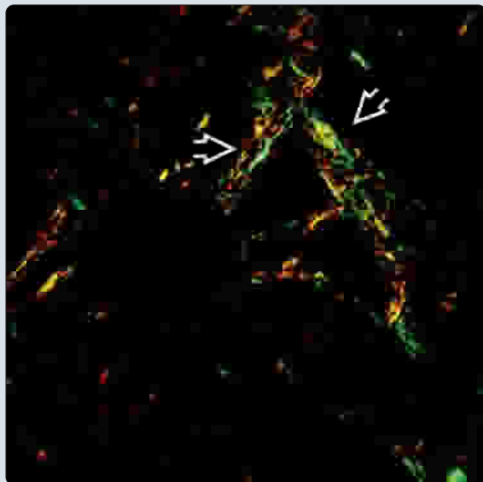
(Left) Amyloid goiter with nodular deposition of amyloid that appears eosinophilic and acellular . **(Right)** The light microscopic appearance of amyloid includes nodular deposition of acellular and amorphous eosinophilic appearing material  within the stroma as well as concentrically around endothelial-lined blood vessels .

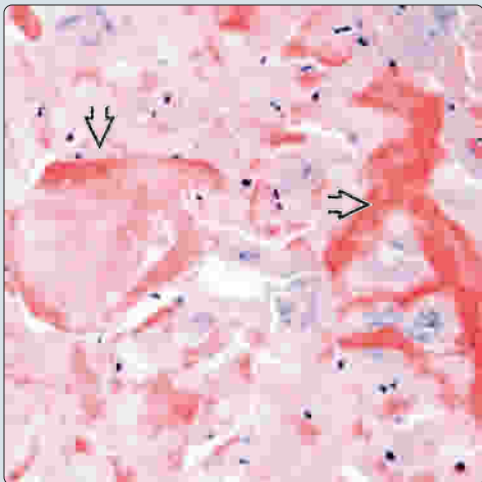


Stromal and Perivascular Amyloid Deposition

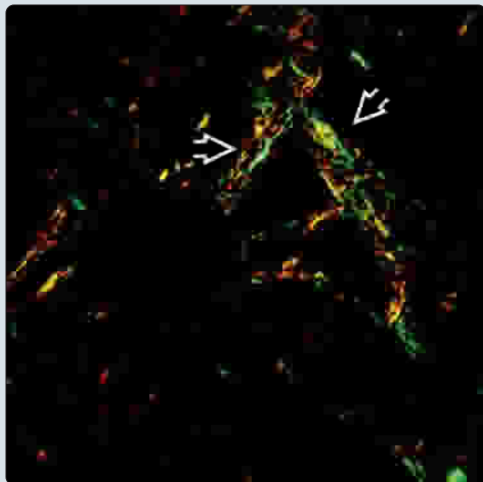


Congo Red Staining

(Left) Irrespective of the setting in which amyloid deposition occurs (e.g., primary amyloidosis, secondary amyloidosis, other), the staining quality of amyloid remains the same and includes Congo red positivity . **(Right)** Congo red staining with polarization in amyloid goiter shows the characteristic apple-green birefringence  that is associated with amyloid deposition irrespective of its site of occurrence.



Apple-Green Birefringence



TERMINOLOGY

Definitions

- Symptomatic mass or clinically detectable thyroid enlargement due to amyloid deposition
 - Amyloid deposits represent extracellular accumulation of fibrillar proteins
 - Identified in association with variety of clinical settings occurring in varied tissue sites
 - Amyloidosis may manifest in several forms including
 - Systemic amyloidosis (primary and secondary)
 - Multiple myeloma-associated amyloidosis
 - Localized or solitary amyloidosis
 - Familial amyloidosis

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Classification of amyloidosis includes
 - Systemic amyloidosis (primary and secondary)
 - Chemical composition: IgG light chain (κ or λ) origin (AL)
 - Chemical composition: Serum amyloid A (SAA)
 - Myeloma-associated amyloidosis
 - Chemical composition: IgG light chain (κ or λ) origin (AL)
 - Localized or solitary amyloidosis
 - Chemical composition: IgG light chain (κ or λ) origin (AL)
 - Familial Mediterranean fever
 - Chemical composition: Serum amyloid A (SAA)
 - Familial amyloidosis
 - Chemical composition: Transthyretin (TTR; prealbumin)
 - Senile amyloidosis
 - Chemical composition: Transthyretin (TTR; prealbumin)
 - Dialysis-associated amyloidosis
 - Chemical composition: B₂-microglobulin ($\text{A}\beta_{2\text{M}}$)
- Most common setting of amyloid in thyroid is in association with medullary thyroid carcinoma
- Amyloid deposition in thyroid can occur as part of
 - Primary amyloidosis
 - Defined as not being associated with underlying chronic disease
 - Amyloid deposition is in a variety of viscera, including heart, gastrointestinal tract, tongue
 - Secondary amyloidosis
 - Defined as being associated with underlying chronic disease
 - Amyloid deposition in kidneys, adrenal glands, liver, and spleen
- More commonly seen as part of secondary systemic amyloidosis
 - In this setting, amyloid is usually found at autopsy rather than resulting in symptomatic mass
- Predisposing disorders associated with secondary systemic amyloidosis with deposition in thyroid include
 - Chronic inflammatory diseases including infections

- Chronic osteomyelitis, pulmonary tuberculosis, chronic bronchitis with bronchiectasis, chronic peritonitis
- Rheumatoid arthritis
- Familial Mediterranean fever
- Crohn disease
- Hodgkin disease
- Extramedullary plasmacytoma (EMP) either as
 - Solitary plasma cell tumor (primary EMP)
 - Manifestation of multiple myeloma (secondary EMP)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very rare
- Age
 - No specific age range
- Sex
 - Equal gender distribution

Site

- Anywhere in thyroid gland

Presentation

- In symptomatic amyloid goiter, clinical presentation includes
 - Nontender, rapidly enlarging neck mass
 - May be associated with dysphagia, dyspnea, and hoarseness

Laboratory Tests

- Patients are euthyroid
 - Thyroid dysfunction not generally present
 - Amyloid deposition may be so extensive as to result in hypothyroidism
 - May rarely be associated with hyperthyroidism
- In association with medullary thyroid carcinoma
 - Serum calcitonin levels elevated

Treatment

- Surgical approaches
 - In symptomatic patients, thyroidectomy (partial or total) is treatment of choice

Prognosis

- Prognosis in relationship to amyloid deposition in thyroid gland is excellent
 - Patient deaths may occur
 - Due to specific organ failure secondary to amyloid deposition (cardiac, renal, or hepatic failure)
- Prognosis in relationship to amyloid deposition in setting of medullary thyroid carcinoma (MTC) correlates with that of MTC

MACROSCOPIC

General Features

- Enlarged glands with nodular to diffuse appearance
 - Weighs 25-300 grams
- Cut surface is white to tan
 - Rubbery to firm consistency

MICROSCOPIC**Histologic Features**

- Diffuse amyloid deposition usually seen, but focal (nodular) deposits may occur
- In diffuse deposition
 - Amyloid evenly distributed throughout gland
 - Replaces thyroid parenchyma
- In nodular deposition
 - Amyloid focally seen
 - Replaces gland in areas of deposition
 - Uninvolved gland appears essentially unremarkable
- Amyloid deposition
 - Appears as extracellular eosinophilic, acellular, amorphous material
 - Degree of amyloid deposition may vary from moderate to extensive
- Amyloid seen in both perifollicular and interfollicular locations compressing follicles
 - Residual follicles vary in appearance
 - From elongated with normal colloid content to slit-like atrophic follicles without colloid
 - Follicular epithelial cells generally appear as flat single cells
 - Squamous metaplasia may be seen
- Amyloid deposition seen around vascular spaces ("angiocentric")
 - Vascular-related amyloid does not result in any functional compromise of involved vascular space
 - Less often, present within walls of vascular spaces
- Additional associated findings may include
 - Chronic lymphocytic thyroiditis
 - Foreign body-type giant cell reaction
 - Mature fat (focal, diffuse)
 - Papillary thyroid carcinoma

ANCILLARY TESTS**Cytology**

- Aspirated material contains
 - Few cells (paucicellular)
 - Small fragments of cyanophilic material (amyloid)
 - Amyloid is congophilic

Histochemistry

- Stains for amyloid
 - Congo red, crystal violet, thioflavin-T positive
 - Red appearance
 - Apple-green birefringence seen under polarized light

Immunohistochemistry

- Positive reactivity with amyloid A (AA) antibody
- In absence of medullary thyroid carcinoma
 - Calcitonin, neuroendocrine markers reactivity not present

Electron Microscopy

- Nonbranching fibrils varying in size from 50-150 Å in diameter

DIFFERENTIAL DIAGNOSIS**Medullary Thyroid Carcinoma**

- Presence of neuroendocrine neoplastic cellular proliferation
- Immunoreactivity for calcitonin, neuroendocrine markers
- Amyloid deposition limited to area(s) of neoplastic proliferation
 - Not distributed in a diffuse pattern as seen in amyloid goiter

Adenomatoid Nodules With Degenerative Changes

- Degenerative changes seen in adenomatoid nodules may include irregular fibrosis
- Fibrosis may be located: Within lesion (intralesional); along periphery suggesting encapsulation; both intralesional and along periphery
- Amyloid may be mistaken for fibrous tissue seen in association with many thyroid diseases
- Fibrosis negative for Congo red and amyloid immunoreactivity

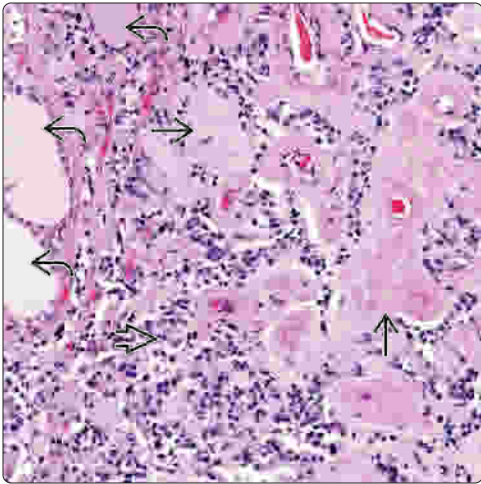
Hyalinizing Trabecular Adenoma

- Considered variant of follicular adenoma
- Characterized by presence of
 - Trabecular to organoid (paraganglioma-like) growth
 - Fibrovascular stroma
 - Extracellular hyalinization that may be prominent and excessive, simulating amyloid
 - Neoplastic cellular proliferation showing
 - Elongated cells with nuclei that display morphologic similarities to papillary thyroid carcinoma
 - Nuclei oriented perpendicular to fibrovascular stroma
 - Perinucleolar halos and cytoplasmic (yellow) inclusions
- Hyalinized stroma negative for Congo red and amyloid immunoreactivity

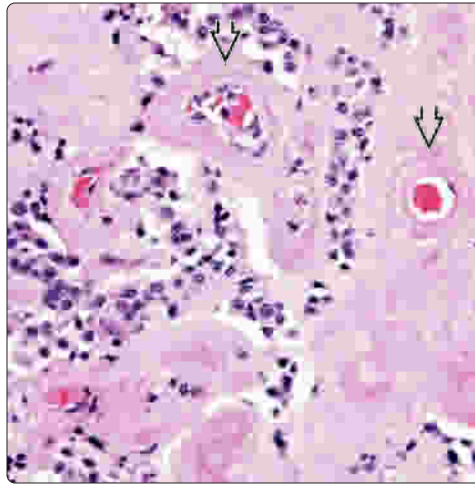
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Amyloid in Medullary Thyroid Carcinoma

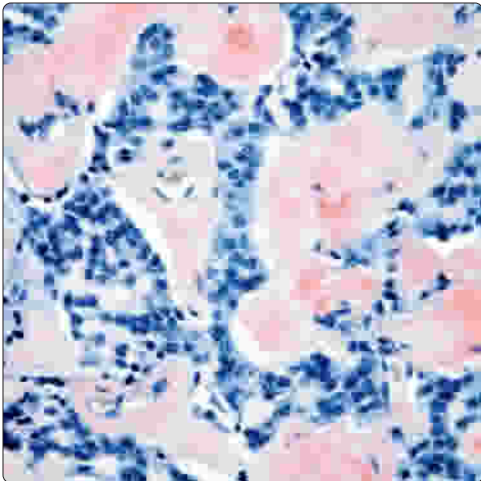


Perivascular Amyloid Deposition

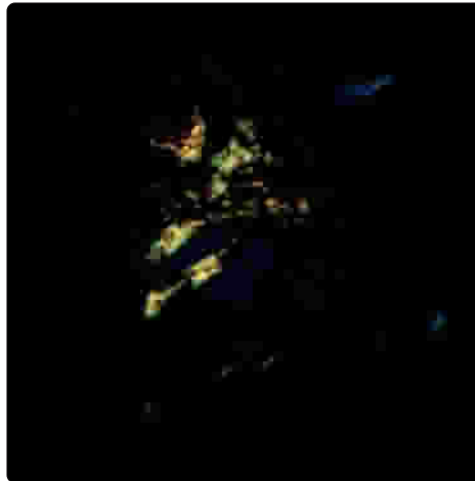


(Left) Medullary carcinoma with associated amyloid deposition appearing as eosinophilic, acellular extracellular material. The amyloid replaces thyroid parenchyma although residual colloid-filled follicles are present. (Right) Amyloid deposition in medullary thyroid carcinoma is present around blood vessels. The tumor cells are characterized by dispersed (salt and pepper) nuclear chromatin. Immunostaining of the tumor cells included calcitonin and neuroendocrine markers (not shown).

Congo Red Staining

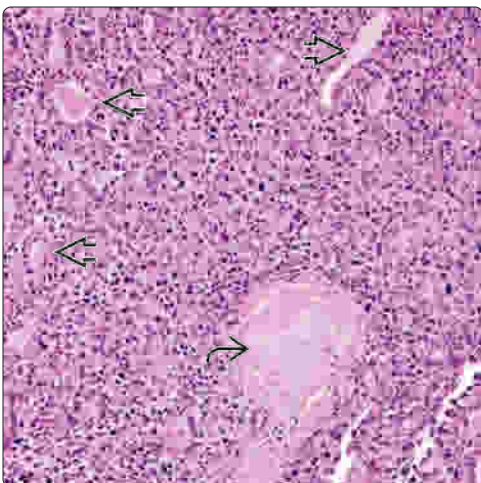


Apple-Green Birefringence

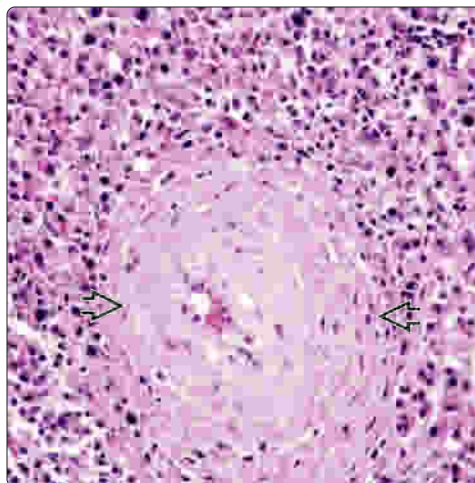


(Left) The amyloid deposition intermixed with the lesional cells of the medullary thyroid carcinoma and around blood vessels is positive by Congo red staining. (Right) Amyloid deposition in medullary thyroid carcinoma shows characteristic apple-green birefringence by Congo red staining with polarization. The characteristic apple-green birefringence associated with amyloid deposition is present irrespective of the site of occurrence but if needed, immunostaining for amyloid A can be used for confirmation (not shown).

Amyloid in Systemic Multiple Myeloma



Perivascular Amyloid Deposition



(Left) Systemic multiple myeloma with involvement of the thyroid gland shows nodular amyloid deposition. Residual colloid-filled follicles are present, but the thyroid tissue is replaced by a hypercellular (plasma cell) infiltrate. (Right) The amyloid deposition occurring in association with myelomatous involvement of the thyroid gland shows perivascular localization. Congo red stain was positive and demonstrated apple-green birefringence (not shown).

Pigments and Crystals in Thyroid Gland

KEY FACTS

TERMINOLOGY

- Intrathyroidal deposition of endogenous or exogenous material including
 - Iron
 - Lipofuscin
 - Degradation products of minocycline
 - Referred to as black thyroid
 - Crystals

ETIOLOGY/PATHOGENESIS

- **Iron deposition**
 - Follows hemorrhage with release of iron from red cells
- **Lipofuscin**
 - Represents degenerative (aging) phenomenon
- **Minocycline deposition**
 - Results from degradation products of tetracycline



CLINICAL ISSUES

- No dysfunction or functional compromise of follicular cells

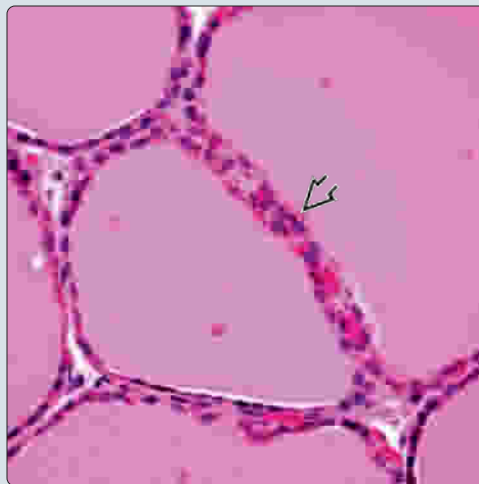
- No treatment needed and no prognostic impact

MICROSCOPIC

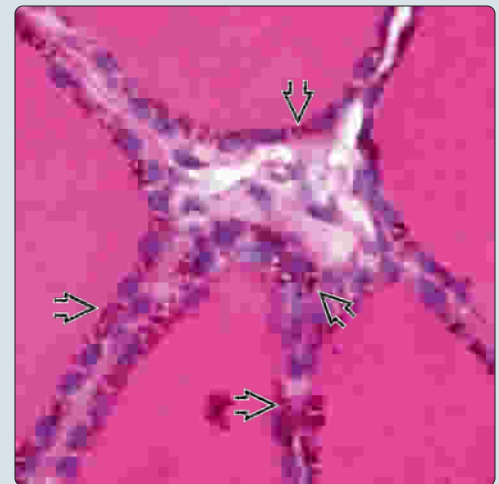
- **Iron deposition**
 - Hemosiderin found in macrophages, within stromal tissues, or within follicular epithelial cells appearing as coarse brown to yellow pigment
- **Lipofuscin deposition**
 - Seen within cytoplasm of follicular epithelial cells appearing as small, yellow to light brown, granular-appearing pigment
- **Minocycline deposition**
 - Appears within cytoplasm of follicular epithelial cells as granular and black
- **Crystals**
 - Intrathyroidal crystals exclusively found within colloid varying in size and shape




(Left) Black thyroid includes the presence of granular and black-appearing pigment in the cytoplasm of follicular epithelial cells . The pigment can be seen in normal thyroid parenchymas as well as in a variety of pathologic (nonneoplastic, neoplastic) thyroid lesions. **(Right)** Adenomatoid nodule with intracytoplasmic deposition of pigmented material with granular appearance is shown. The pigment  in the thyroid epithelial cells represents an incidental finding, requiring clinical correlation to a history of minocycline use.

Pigment in Nonlesional Follicular Cells



Pigment in Follicular Cells of Adenomatoid Nodule

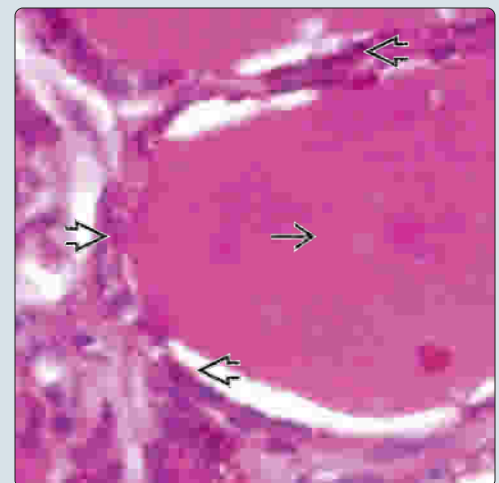


(Left) The pigment associated with black thyroid stains with Fontana appears as dark black granules  within the cytoplasm of follicular epithelial cells. **(Right)** The pigment associated with black thyroid stains with PAS appears as reddish-brown granules  within the cytoplasm of follicular epithelial cells. PAS is also a good stain for colloid . In spite of the pigment deposition, there is no dysfunction or functional compromise of the follicular cells.

Fontana Staining



Periodic Acid-Schiff (PAS) Staining



TERMINOLOGY

Definitions

- Intrathyroidal deposition of endogenous or exogenous material including
 - Iron
 - Lipofuscin
 - Degradation products of minocycline
 - Referred to as black thyroid
 - Crystals

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- **Iron deposition**
 - Follows hemorrhage with release of iron from red blood cells
 - Resorption takes place and iron is converted to hemosiderin
 - Hemosiderin stored in cell cytoplasm of phagocytizing cells (macrophages)
 - Rarely, iron stored in thyroid as component of disorder of iron metabolism rather than secondary to hemorrhage
- **Lipofuscin**
 - Represents degenerative (aging) phenomenon
 - True nature yet to be determined
 - Contains histidine and tryptophan
 - In thyroid gland, lipofuscin pigment can be seen within follicular epithelial cells, including nonneoplastic lesions and neoplasms
- **Minocycline deposition**
 - Results from degradation products of tetracycline
 - Tetracycline derivative administered to adults for treatment of various conditions (infections, acne)
 - May cause black pigmentation and discoloration of various sites including
 - Skin
 - Thyroid gland
 - Shares histochemical, electron microscopic, and elemental analysis features with lipofuscin
 - True makeup not fully known; possibilities include
 - Degradation products of drug combined with lipofuscin
 - Oxidation degradation of drug itself
 - Drug interaction and alteration of tyrosine metabolism
 - Lysosomal dysfunction
- **Crystals**
 - Composed of calcium oxalate

CLINICAL ISSUES

Epidemiology

- Incidence
 - Not known
- Age
 - Typically but not exclusively in (older) adults
 - Particularly in association with iron deposition
 - Frequency of finding crystals within thyroid gland appears to increase with age

- Sex
 - Equal gender distribution

Presentation

- **Iron deposition**
 - Represents incidental finding
 - Reflects secondary phenomenon due to hemorrhage
 - Identified following traumatic (e.g., post fine-needle aspiration biopsy) &/or degenerative changes
- **Lipofuscin deposition**
 - Incidental finding
- **Minocycline deposition**
 - Incidental finding
 - Not associated with glandular enlargement (hyperplasia) or functional abnormalities of gland
 - Rarely, patients may be hypothyroid but no specific link to minocycline deposition
- **Crystals**
 - Incidental finding
 - Increased frequency of intracolloidal crystals found in patients undergoing hemodialysis for chronic renal failure

Laboratory Tests

- No associated dysfunction or functional compromise of thyroid follicular cells

Treatment

- Options, risks, complications
 - No specific treatment needed or recommended

Prognosis

- No impact on prognosis

MICROSCOPIC

Histologic Features

- **Iron deposition**
 - Hemosiderin found in macrophages, within stromal tissues, or within follicular epithelial cells appears as coarse brown to yellow pigment
 - Iron stains (Prussian blue, Mallory) can be used for identification and to distinguish from other pigments
- **Lipofuscin deposition**
 - Pigment seen within follicular epithelial cells
 - Intracytoplasmic accumulation of small yellow to light brown granular-appearing pigment
- **Minocycline deposition**
 - Appears within cytoplasm of follicular epithelial cells as granular and black
 - Also seen within follicle lumina as large black deposits admixed with colloid
 - Can be incidental finding in wide variety of thyroid pathologic conditions (nonneoplastic lesions, neoplasms)
 - Localization of pigment may vary including
 - In pathologic lesion but not in normal thyroid parenchyma
 - In normal thyroid parenchyma but not in pathologic lesion
 - In both pathologic lesion and normal thyroid parenchyma
- **Crystals**

Pigments and Crystals in Thyroid Gland

- Intrathyroidal crystals exclusively found within colloid
 - Do not appear within cytoplasm of follicular epithelial cells or in stromal tissues
- Crystals readily apparent by light microscopy varying in size and shape
 - Polarization enhances their detection
- Finding of intracoloidal crystals is not associated with any specific diagnosis
 - May be found in virtually all thyroid abnormalities
 - Highest prevalence of crystals occurs in association with benign diseases
 - Most commonly seen in nodular goiters followed by follicular adenomas
 - May be found in association with malignant tumors (e.g., papillary carcinoma, follicular carcinoma), but prevalence is low
 - Low prevalence in association with Graves disease, lymphocytic thyroiditis, subacute thyroiditis
- Chemical analysis shows crystals to be composed of calcium oxalate
 - Thyroglobulin (-)
 - S100 protein, melanocytic markers (HMB-45, Melan-A, tyrosinase) all negative
- Seen in association with metastatic malignant melanoma to thyroid
 - May be isolated metastasis or part of widespread metastatic disease
 - Argentaffin (+)
 - PAS(-)
 - Neoplastic cells immunoreactive for
 - S100 protein
 - HMB-45
 - Melan-A
 - MITF1
 - Tyrosinase
 - SOX10
 - Vimentin

ANCILLARY TESTS

Cytology

- Crystals may be found by fine-needle aspiration
 - Occurrence in fine-needle cytology lower than that in histologic specimens

Histochemistry

- **Iron deposition**
 - Prussian blue, Mallory stains
 - Appears blue
 - Used to identify iron and distinguish it from other pigments
- **Lipofuscin deposition**
 - Lipid (Sudan IV) and lipofuscin stains
 - Diastase-sensitive, PAS(+) intracytoplasmic material
 - Iron staining is absent
- **Minocycline**
 - Positive staining with
 - PAS
 - Lipid stains
 - Lipofuscin stains
 - Argentaffin stains (Fontana) may be positive
 - Iron staining negative

DIFFERENTIAL DIAGNOSIS

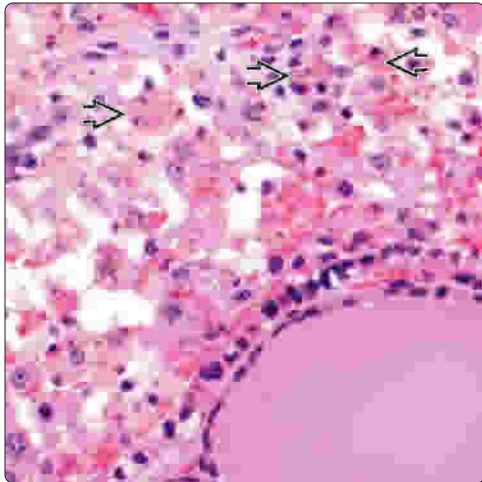
Melanin

- Melanin rarely found in thyroid
- Seen in association with medullary thyroid carcinoma, melanocytic variant
 - Argentaffin (+)
 - PAS(-)
 - Neoplastic cells
 - Calcitonin (+)
 - Chromogranin (+)
 - Synaptophysin (+)
 - CD56(+)
 - TTF-1(+)
 - Cytokeratins (+)

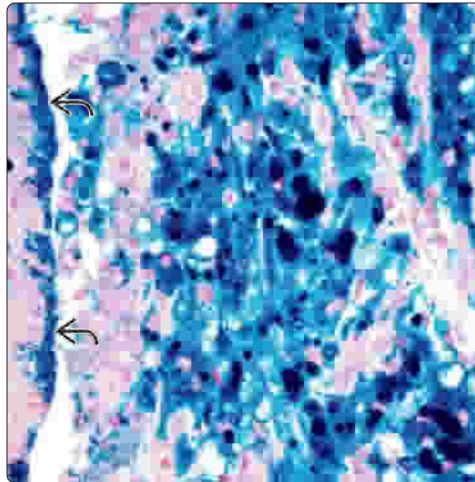
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Hemosiderin Deposition

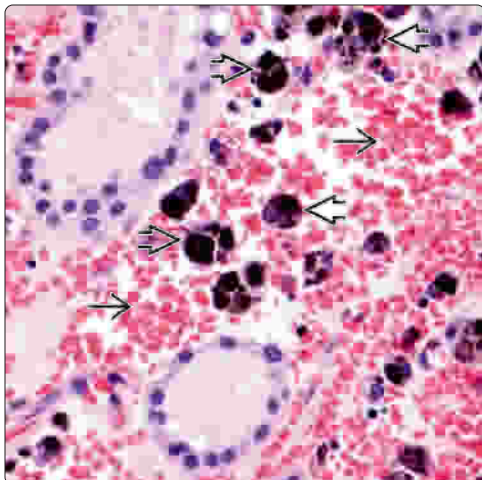


Iron Staining

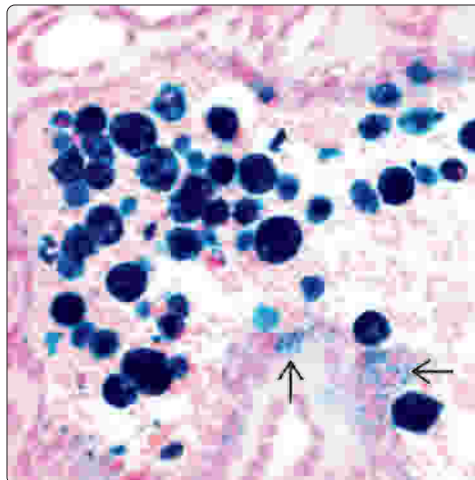


(Left) Adenomatoid nodule with degenerative alterations due to trauma (e.g., post fine-needle aspiration) or occurring spontaneously may result in hemorrhage, including hemosiderin deposition within macrophages appearing as coarse brown to yellow pigment [1]. (Right) In addition to the macrophages, iron staining shows the presence of hemosiderin within the cytoplasm of follicular epithelial cells [2]. In spite of the intracytoplasmic pigment, there is no compromise of the functional integrity of the follicular cells.

Histiocytes With Hemosiderin

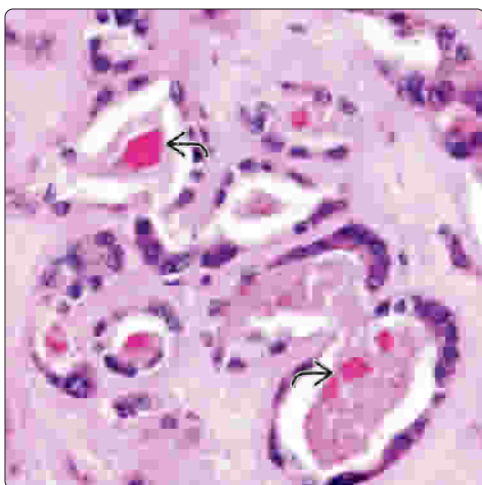


Iron Staining

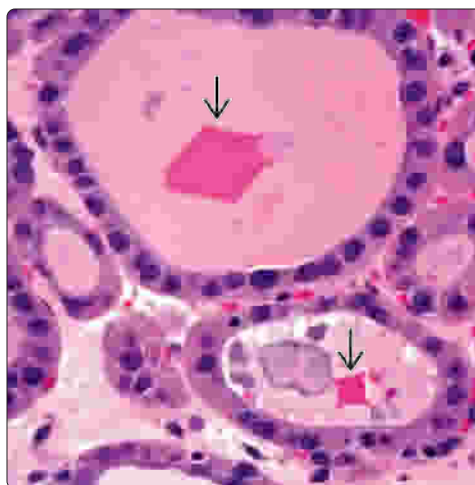


(Left) Resected follicular adenoma following preoperative fine-needle aspiration shows the presence of fresh [1] and remote hemorrhage, the latter characterized by hemosiderin deposition within macrophages appearing as coarse brown pigment [2]. (Right) Iron staining in a follicular adenoma confirms the presence of hemosiderin appearing as intensely blue material within the cytoplasm of macrophages. Focally, iron-positive hemosiderin is present within the cytoplasm of follicular cells [3].

Crystals in Adenomatoid Nodule



Crystals in Follicular Adenoma



(Left) Adenomatoid nodule with intrafollicular crystals [1], varying in size and shape, are composed of calcium oxalate and are exclusively found within colloid and not follicular epithelial cells. They are most commonly found in adenomatoid nodules and follicular adenomas. (Right) Follicular adenoma, oncocyctic variant, shows the presence of intrafollicular crystals of varying size and shape [2]. The crystals represent incidental findings and are of no diagnostic or prognostic import.

Post Fine-Needle Aspiration Changes

KEY FACTS

TERMINOLOGY

- Reactive &/or degenerative morphologic alterations in thyroid lesions following fine-needle aspiration biopsy (FNAB)
- Synonym: Worrisome histologic alterations following fine-needle aspiration of thyroid (WHAFFT)

ETIOLOGY/PATHOGENESIS

- Iatrogenically induced
 - Most often secondary to fine-needle aspiration biopsy
- Lesions/tumors with cytoplasmic oxyphilia (so-called Hürthle cells) more prone to retrogressive changes following FNAB

CLINICAL ISSUES

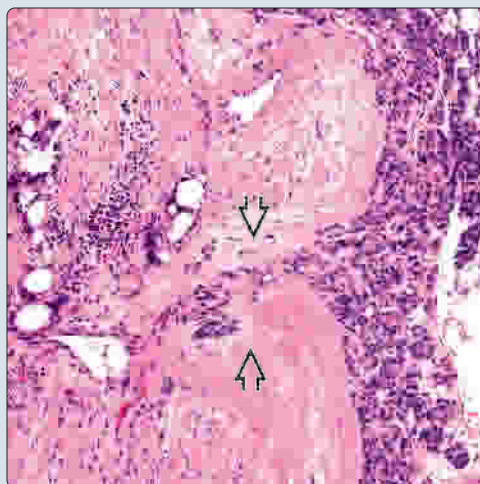
- Common occurrence
- Occurs in all ages
- No specific localization
- Prognosis dependent on nature of underlying lesion

MICROSCOPIC

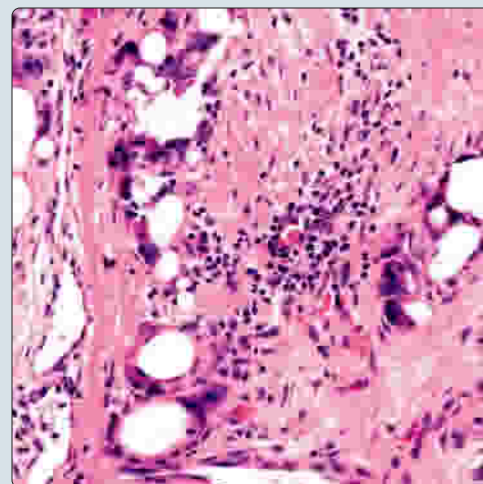
- **Acute changes:** Usually identified within 3 weeks following FNAB
 - Most common findings include hemorrhage, granulation tissue
- **Chronic changes:** Usually identified > 3 weeks from FNAB to surgical removal and include
 - Infarction
 - Metaplasia (squamous, oxyphilic)
 - Capsular alterations with pseudoinvasive growth
 - Vascular alterations (e.g., dilated vascular spaces with thrombosis, organization &/or papillary endothelial hyperplasia), endothelial cell atypia
- Postoperative spindle cell nodule/proliferation
 - Exuberant proliferation of spindle cells with bland cytology and numerous mitoses
 - May suggest diagnosis of anaplastic carcinoma or sarcoma

Post-FNAB Needle Tract

(Left) The appearance at low magnification of this encapsulated follicular adenoma (right side of image) includes a linear-appearing "bud" into the fibrous capsule, suggesting capsular invasion. **(Right)** At higher magnification, the needle tract "bud" includes mixed inflammatory cells, multinucleated giant cells, and hemorrhage rather than follicular epithelial cells. This supports the presence of pseudoinvasion rather than true capsular invasion.

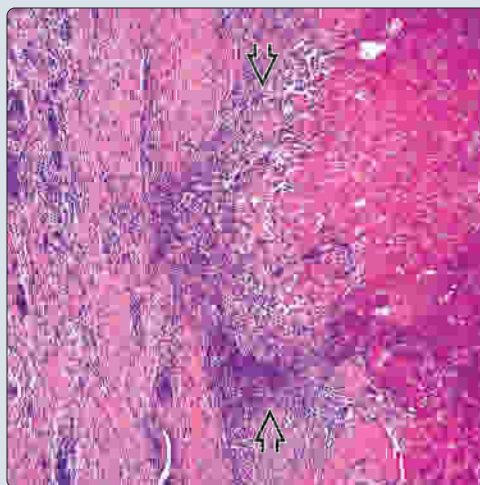


Inflammatory Cells

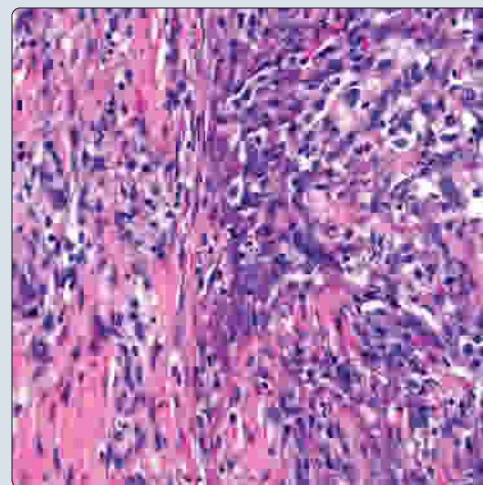


Post-FNAB Infarcted Tumor and Needle Tract

(Left) Fine-needle aspiration biopsy (FNAB) of this follicular adenoma (oncocytic variant) resulted in tumor infarction (right side of image) as well as the appearance at low magnification of possible invasion of the fibrous capsule by the tumor, suggesting a possible diagnosis of follicular carcinoma. **(Right)** At higher magnification, the cellular component seen within the capsule includes an admixture of acute and chronic inflammatory cells rather than follicular epithelial cells, excluding the diagnosis of a follicular carcinoma.



Acute and Chronic Inflammation



TERMINOLOGY

Synonyms

- Worrisome histologic alterations following fine-needle aspiration of thyroid (WHAFFT)

Definitions

- Reactive &/or degenerative morphologic alterations in thyroid lesions following fine-needle aspiration biopsy (FNAB)

ETIOLOGY/PATHOGENESIS

Iatrogenic

- Fine-needle aspiration biopsy has tremendous utility as 1st interventional procedure in diagnosis of thyroid masses
- Diagnostic sensitivity and specificity of FNAB for thyroid mass is high
- In most instances (with some exceptions), surgical removal is treatment for thyroid lesion irrespective of diagnosis by FNAB
- Post-FNAB histologic changes occur in numerous lesions, including
 - Nonneoplastic lesions
 - Adenomatoid nodules
 - Hyperplastic lesions (e.g., Graves disease, others)
 - Neoplasms
 - Follicular adenoma and variants
 - Follicular carcinoma and variants
 - Papillary thyroid carcinoma and variants
 - Medullary thyroid carcinoma and variants
- Lesions/tumors with cytoplasmic oxyphilia (so-called Hürthle cells)
 - More prone than other cell types to retrogressive changes following FNAB
 - Due to high content of oxygen-sensitive mitochondria, oncocytic (Hürthle cells) are more easily traumatized
 - Potentially results in infarction and additional degenerative changes

CLINICAL ISSUES

Epidemiology

- Incidence
 - Common occurrence
- Age
 - Occurs in all ages
- Sex
 - Equal gender distribution

Site

- No specific localization

Prognosis

- Dependent on nature of underlying lesion
- Histologic alterations caused by FNAB may lead to erroneous diagnosis
 - Change in interpretation from benign process to malignant

MICROSCOPIC

Histologic Features

- FNAB may result in number of reactive histologic changes in resected thyroid gland
- Based on type of reaction seen, post-FNAB alterations may include acute or chronic type changes
- **Acute changes**
 - Usually identified within 3 weeks following FNAB
 - Most common findings include
 - Fresh hemorrhage
 - Remote hemorrhage in form of hemosiderin-laden macrophages
 - Granulation tissue
 - Other alterations may include
 - Localized follicular destruction
 - Capsular alterations
 - Reactive nuclear atypia includes enlargement with clearing of nuclear chromatin; typically occurs near needle tract
 - Necrosis and mitoses
- **Chronic changes:** Usually identified > 3 weeks from FNAB to surgical removal and include
 - Fibrosis
 - Infarction
 - Metaplasia (squamous, oncocytic)
 - Capsular alterations with pseudoinvasive growth
 - May take form of needle tract with linear hemorrhagic tract
 - May suggest presence of capsular invasion
 - Key findings include absence of follicular epithelium within needle tract with associated chronic inflammatory cell infiltrate and hemorrhage (recent and remote)
 - Vascular alterations include
 - Artifactual implantation or invasion of tumor cells, including cells floating within vascular lumina rather than adherent to vessel wall
 - Dilated vascular spaces with thrombosis, organization &/or papillary endothelial hyperplasia (Masson tumor-like reaction)
 - Endothelial cell atypia
- Post-FNAB alterations of adenomatoid nodules may include
 - Cyst formation with or without papillae
 - Fibrosis and calcifications
 - Cholesterol granuloma formation
 - Nuclear atypia
- Post-FNAB alterations of lesions with oncocytic cells (so-called Hürthle cells)
 - Oxyphilic cells occur in all settings (e.g., metaplasia, follicular adenoma, follicular carcinoma, papillary carcinoma)
 - Changes include hemorrhage (recent, remote), infarction, necrosis, papillary architecture
- Post-FNAB infarcted follicular adenoma
 - Infarction may be partial or complete
 - Infarction appears as coagulative necrosis with associated hemorrhage and inflammatory cell infiltrate
 - Infarction may compromise histology, making recognition of nature of lesion difficult

- Peripheral rim of residual, viable tumor may be present, which may show marked reactive nuclear atypia
- In infarcted foci, architectural pattern of lesion is retained despite cellular necrosis
- With time, granulation tissue and macrophages may be present
- Postoperative spindle cell nodule/proliferation
 - Exuberant proliferation of spindle cells with bland cytology and numerous mitoses
 - May suggest diagnosis of anaplastic carcinoma, sarcoma
 - Nodular, relatively circumscribed &/or nonencapsulated
 - Often limited to central part of preexisting thyroid lesion(s)
 - Variable cellularity with mild nuclear pleomorphism, rare mitotic figures
 - Plump spindle cells with rich network of thin-walled blood vessels and chronic inflammatory cell component

ANCILLARY TESTS

Histochemistry

- Periodic acid-Schiff (PAS)
 - Stains colloid red
 - May be helpful in recognizing lesion as follicular epithelial neoplasm

Immunohistochemistry

- Thyroglobulin, TTF-1
 - Follicular epithelial cell lesion/tumor will be positive
 - In cases showing infarction, antigenicity is retained in infarcted lesional cells
- Calcitonin, neuroendocrine markers
 - C-cell derived lesions/tumor positive
 - In spite of degenerative changes, antigenicity is retained in lesional cells
- Smooth muscle actin
 - Diffusely positive in spindle cells of postoperative spindle cell proliferation
 - Suggests myofibroblastic origin

DIFFERENTIAL DIAGNOSIS

Vascular Neoplasm

- Reactive vascular alterations may suggest presence of vascular tumor
 - Post-FNAB vascular changes may include
 - Widely dilated and blood-filled spaces
 - Papillary endothelial hyperplasia
- Intrathyroidal vascular tumors may include
 - Hemangioma, angiosarcoma
- Factors that may be helpful in not misdiagnosing reactive vascular alterations for thyroid vascular neoplasm include
 - Rarity of primary vascular neoplasms occurring in thyroid gland
 - Presence of other post-FNAB reactive (nonvascular) alterations
 - Temporal sequence from FNAB to surgical removal
 - Typically relatively short interval from time of FNAB to resection

- Knowledge that recent preoperative FNAB occurred helpful in considering changes as being reactive rather than neoplastic

Papillary Thyroid Carcinoma

- Shows constellation of diagnostic nuclear features that are absent in post-FNAB alterations

Undifferentiated (Anaplastic) Thyroid Carcinoma

- Densely cellular proliferation with
 - Marked nuclear pleomorphism, increased mitotic activity, atypical mitoses, necrosis, invasive growth
- Characteristic demographics and clinical history
 - Predilection for older adults
 - Clinical history of rapidly enlarging neck mass often in longstanding thyroid lesion
 - Some cases may occur in absence of longstanding thyroid lesion

Sarcoma

- Rare neoplastic type in thyroid gland that may include
 - Angiosarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor (malignant Schwannoma)
- Sarcomas typically characterized by
 - Densely cellular proliferation with marked nuclear pleomorphism, increased mitotic activity, atypical mitoses, necrosis
- Immunohistochemical staining helpful in diagnosis, including
 - Angiosarcoma: CD31, CD34, factor VIII-related antigen, ERG, FLI1
 - Leiomyosarcoma: Smooth muscle actin
 - Malignant peripheral nerve sheath tumor (MPNST) S100 protein and SOX10 variably present
 - Low-grade MPNST diffusely reactive
 - High-grade MPNST typically absent to focally reactive

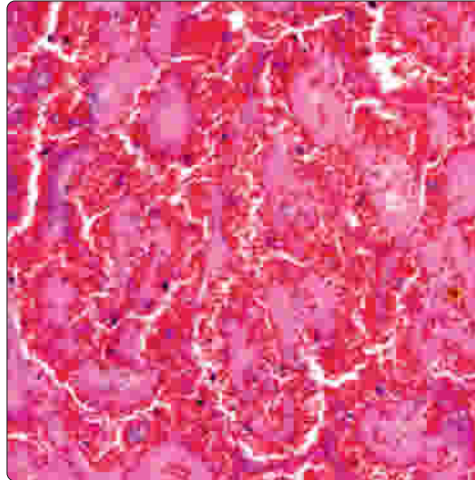
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Adenomatoid Nodule With Thrombi

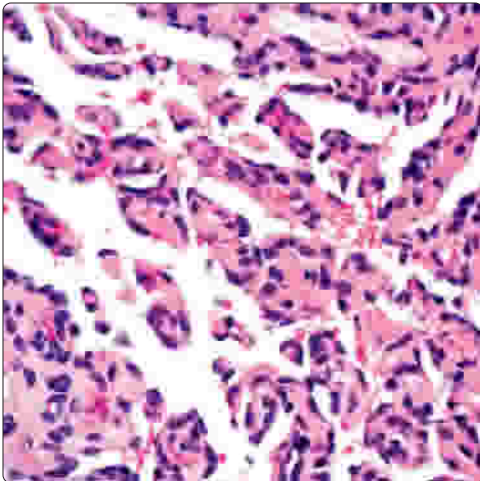


Post-Aspiration Vascular Alterations

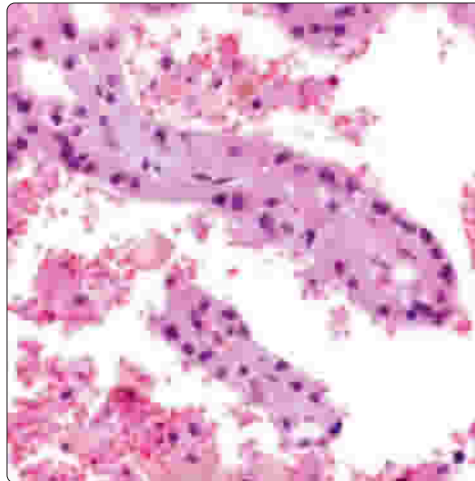


(Left) A dominant adenomatoid nodule shows thrombi lying within cystically dilated spaces [E]. These changes were identified in the thyroidectomy that followed a few weeks after a FNAB. The gross findings are not particularly worrisome for a vascular neoplasm. *(Right)* Post-aspiration vascular alterations include dilated and blood-filled endothelial-lined vascular spaces that suggest the possibility of a vascular neoplasm, such as a hemangioma.

Papillary Endothelial Hyperplasia

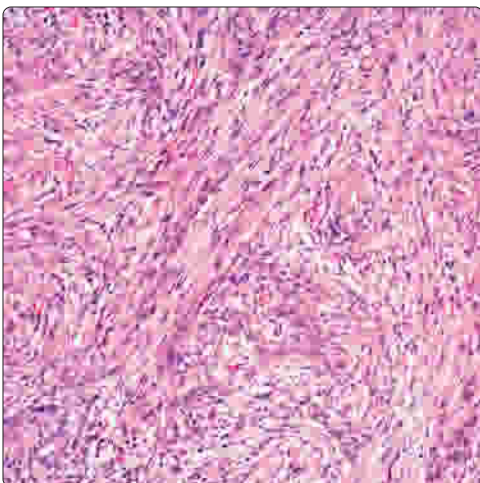


Retrogressive Changes Including Papillae and Hemorrhage

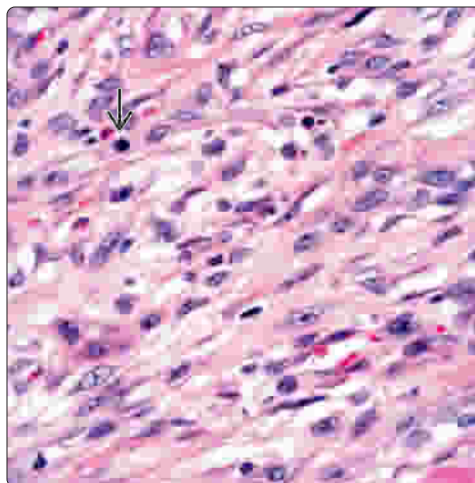


(Left) Post-FNAB papillary endothelial hyperplasia, characterized by the presence of numerous papillae projecting into vascular lumina that are composed of a single layer of endothelium surrounding a collagenized core, is shown here. *(Right)* The papillae occurring secondary to FNAB are wider and less complex than those typically seen in papillary thyroid carcinoma and lack the diagnostic nuclear alterations of papillary thyroid carcinoma. Associated hemorrhage and hemosiderin-laden macrophages are present.

Post-FNAB Spindle Cell Nodule



Post-FNAB Spindle Cell Nodule



(Left) Post-FNAB spindle cell nodule in an adenomatoid nodule (not shown) includes the presence of spindle-shaped cellular proliferation with fascicular to storiform growth and variable sclerotic and myxoid stroma. *(Right)* At higher magnification, mitotic figures may be identified [E]. The spindle-shaped to epithelioid-appearing fibroblasts include enlarged nuclei but lack the cytomorphic features of a malignant cellular proliferation.

KEY FACTS

TERMINOLOGY

- Benign, nonneoplastic increase in C cells within thyroid gland parenchyma
 - Ultimobranchial body gives rise to C cells

CLINICAL ISSUES

- Most frequently concentrated in middle-upper outer zones of both thyroid lobes

MACROSCOPIC

- Sections from mid-upper outer lobes maximize diagnostic opportunity

MICROSCOPIC

- Generally easiest to find adjacent to or intermixed with solid cell nests
- Small cells in a parafollicular distribution
- Cytoplasm is clear, light to bluish, with granularity
- **Physiologic or reactive**
 - Tends to be focal, with only few cells

- Usually, 3-5 cells in small clusters
- 8-10 cell clusters in low power field (40x total magnification)
- May be observed in association with other thyroid conditions or neoplasms

• Neoplastic



- Nodular &/or diffuse proliferation
- No follicle destruction
- Not associated with amyloid or fibrosis
- ≤ 50 cells in an aggregate
- Shows *RET* germline mutations

ANCILLARY TESTS

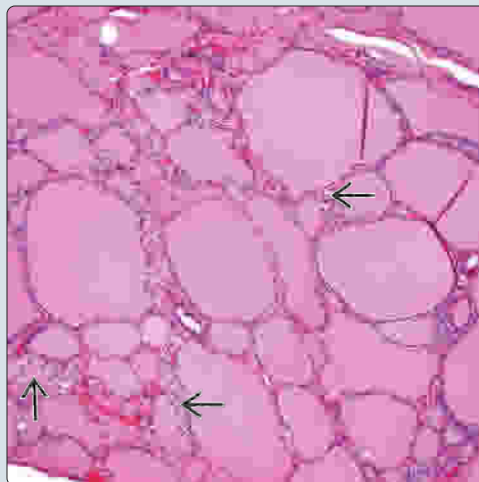
- **Positive:** Calcitonin; CD56, chromogranin, synaptophysin

TOP DIFFERENTIAL DIAGNOSES

- Microscopic medullary carcinoma, microscopic papillary carcinoma, palpation thyroiditis, squamous metaplasia, intraglandular spread of medullary carcinoma



(Left) There is an increased number of C cells  in this gland affected by adenomatoid nodules. There is no follicle destruction and no cytologic atypia. The collections are < 50 cells. **(Right)** The C cells have slightly granular, blue to cleared cytoplasm . They are usually present as single cells or in small clusters of cells in a parafollicular distribution. No cytologic atypia or destruction is present.

Parafollicular C-Cell Increase

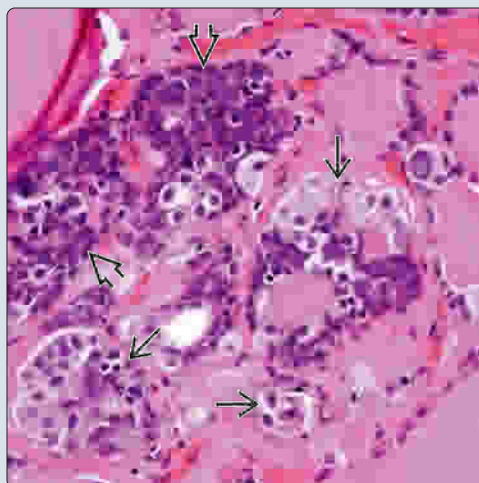


Granular, Blue Cytoplasm of C Cells

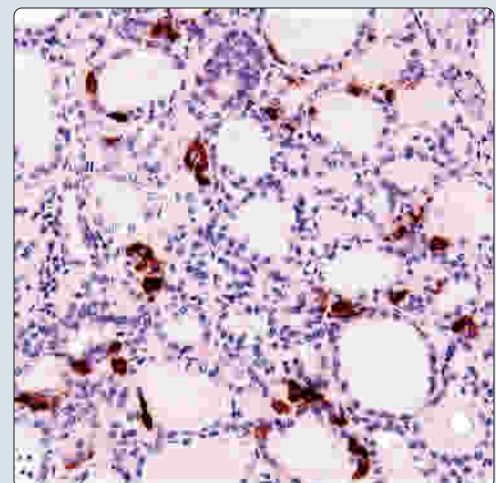


(Left) C cells  are frequently identified in association with solid cell nests , as they are derived from these structures. While there is clustering, there is no destructive growth or amyloid. **(Right)** Calcitonin is the most reliable stain in highlighting the C cells in physiologic C-cell hyperplasia. Synaptophysin and CD56 are also positive but are not as specific.

Solid Cell Nest and C Cells



Calcitonin IHC Highlights C Cells



TERMINOLOGY

Definitions

- Benign, nonneoplastic increase in C cells within thyroid gland parenchyma

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Ultimobranchial body gives rise to C cells
 - Identified in middle to upper thyroid lobes (not isthmus)
 - Neuroendocrine cells with argyrophilic cytoplasmic granules
- C cells ultimately give rise to medullary carcinoma

CLINICAL ISSUES

Epidemiology

- Incidence
 - Unknown, although common if diligently sought

Site

- Most frequently concentrated in middle-upper outer zones of both thyroid lobes

Prognosis

- No adverse outcome for this physiologic process

MACROSCOPIC

Sections to Be Submitted

- Sections from mid-upper outer lobes maximize diagnostic opportunity

Size

- Individual cells to small clusters of cells (< 50 µm)

MICROSCOPIC

Histologic Features

- Generally easiest to find adjacent to or intermixed with solid cell nests
- Small cells in parafoveolar distribution
- Cytoplasm is clear, light to bluish, with granularity
- Nuclei tend to be slightly larger than follicular epithelial cell nuclei
 - No nuclear atypia
- C-cell hyperplasia is separated into subtypes
 - **Physiologic or reactive**
 - Tends to be focal, with only a few cells
 - Usually, 3-5 cells in small clusters
 - 8-10 cell clusters in low-power field (40x total magnification)
 - May be observed in association with other thyroid conditions or neoplasms
 - Advanced age, hypercalcemia, chronic lymphocytic thyroiditis, exogenous estrogen, cimetidine
 - Physiologic response may be to trophic hormones, hypercalcemia, paracrine factors, or inflammation
 - **Neoplastic**
 - Nodular &/or diffuse proliferation
 - Easily identified on H&E stained sections
 - No follicle destruction

- Not associated with amyloid or fibrosis
- ≤ 50 cells in an aggregate
- Conceptually: Medullary carcinoma in situ
- Seen with hereditary medullary carcinoma
- Shows *RET* germline mutations

ANCILLARY TESTS

Immunohistochemistry

- Generally, immunohistochemistry is required to highlight cells
- **Positive:** Calcitonin
- **Positive,** but not as sensitive/specific: CD56, chromogranin, &/or synaptophysin

Genetic Testing

- No *RET* mutations in physiologic C-cell hyperplasia

DIFFERENTIAL DIAGNOSIS

Microscopic Medullary Carcinoma

- Aggregates of > 50 cells
- Thyroid follicle destruction, with breaching of basement membrane
- Fibrosis &/or amyloid may be seen
- Cellular pleomorphism is more easily identified
- *RET* mutations can be detected

Palpation Thyroiditis

- Single or few follicles destroyed (follicle centric)
- Random distribution throughout gland
- Histiocytes and giant cells

Squamous Metaplasia

- Random distribution throughout gland, without parafoveolar distribution
- Paved pattern, with intercellular bridges

Intraglandular Spread of Medullary Carcinoma

- Can be seen throughout gland, accentuated at periphery where vessels have their highest concentration
- Only in lymph-vascular channels (not parafoveolar)
- Pleomorphism present

Microscopic Papillary Carcinoma

- Not in parafoveolar distribution, showing fibrosis or stellate infiltration
- Large cells with high nuclear:cytoplasmic ratio
- Nuclear overlapping, nuclear grooves and irregularities, intranuclear cytoplasmic inclusions

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Follicular Adenoma

KEY FACTS

TERMINOLOGY

- Benign, encapsulated neoplasm of thyroid follicular epithelial cells

CLINICAL ISSUES

- 3-5% of adults
- Most present in 5th-6th decades
- Female >> male (4-5:1)
- Painless thyroid nodule in euthyroid patients
- Lobectomy treatment of choice with excellent long-term prognosis

MACROSCOPIC

- Solitary, well delineated from adjacent parenchyma
- Submit entire peripheral zone (parenchyma to capsule to tumor interface)

MICROSCOPIC

- Encapsulated tumor surrounded by variable thick fibrous connective tissue capsule

- Smooth muscle-walled vessels in fibrosis help to confirm presence of capsule
- Tumor architecture and cytologic appearance distinct from surrounding parenchyma
- Cuboidal to polygonal cells, basal, round, dark nuclei
- Post FNA artifacts are frequent
- Many variants: Oncocytic, lipoadenoma, signet-ring, lipid-rich, clear cell, bizarre nuclei

ANCILLARY TESTS

- FNA cytology does **not** distinguish among adenomatoid nodule, follicular adenoma, or follicular carcinoma
- Positive with keratins, TTF-1, pax-8, thyroglobulin

TOP DIFFERENTIAL DIAGNOSES

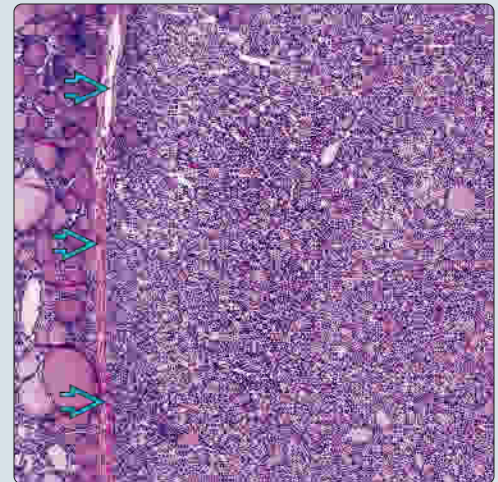
- Follicular carcinoma, papillary carcinoma (follicular variant), medullary carcinoma, adenomatoid nodules, parathyroid adenoma

Encapsulated Adenoma With Fine-Needle Aspiration Effect

(Left) This low-power image demonstrates a follicular neoplasm surrounded by a well-formed, slightly thickened capsule. Colloid is easily identified. There is no evidence of invasion. A fine-needle aspiration (FNA) site is present [X]. (Right) A thin fibrous connective tissue capsule [X] separates a distinct population of follicular cells from the surrounding uninvolved follicular thyroid epithelium.

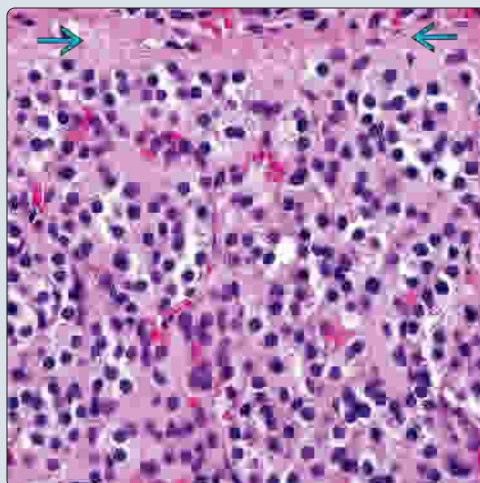


Thin Capsule

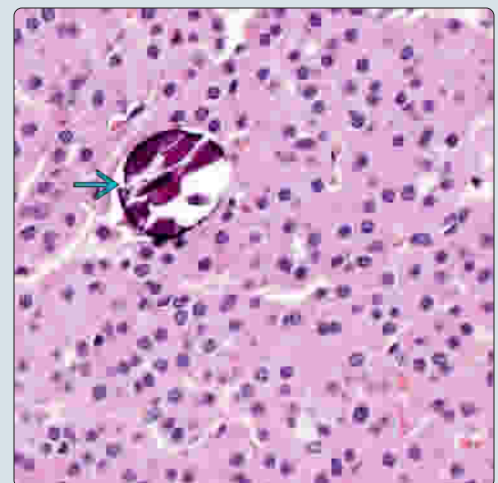


Thin Fibrous Connective Tissue Capsule

(Left) Follicles with scant colloid, surrounded by cuboidal cells with round and regular nuclei, show coarse nuclear chromatin distribution. There is ample eosinophilic cytoplasm. A thin capsule is noted [X]. (Right) Oncocytic tumors, like this adenoma, will often have psammoma-like calcifications [X] within the colloid. They usually do not have laminations, although they may occasionally show laminations, as suggested in this image.



Calcified Secretions



TERMINOLOGY

Abbreviations

- Follicular adenoma (FA)

Definitions

- Benign, encapsulated neoplasm of thyroid follicular epithelial cells
 - Several variant histologies; oncocytic type most common

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Iodine deficiency
 - Nodules are 2-3x more common in low iodine consumption areas
 - May be due to thyroid-stimulating hormone (TSH) stimulation of follicular epithelium
- Radiation (γ radiation specifically)
 - Exposure during childhood and adolescence
 - Increased risk of ~ 15x
 - FA develops 10-15 years after exposure

Inherited Syndrome

- Uncommon, since most adenomas are sporadic
 - Cowden disease: Multiple hamartoma syndrome with germline mutations of *PTEN* tumor suppressor gene (located on 10q23), resulting in loss of *PTEN* function
 - Tumors tend to be bilateral and multiple
 - Carney complex: Autosomal dominant disease caused by germline mutations in *PRKAR1A* gene
 - Tumors often multiple and oncocytic

CLINICAL ISSUES

Epidemiology

- Incidence
 - Difficult to accurately determine, as cellular solitary nodules cannot be separated by noninvasive methods
 - 3-8% of adults have solitary palpable nodules, of which ~ 75% represent adenoma
 - Carcinoma must be excluded, which drives further evaluation
- Age
 - Broad age range, but most present in 5th-6th decades
- Sex
 - Female >> male (4-5:1)

Presentation

- Painless, slow-growing thyroid nodule/mass
 - Mobile, discrete, smooth nodules that move with thyroid
- Identified incidentally during palpation or ultrasound of neck for different reasons
- When large, difficulty swallowing and local compressive symptoms may be seen
- Bleeding into tumor may result in sudden pain, tenderness, and increase in size

Laboratory Tests

- Patients usually euthyroid, with rare hyperfunctional adenomas

Treatment

- Options, risks, complications
 - Previous radiation exposure or family history results in clinical, radiographic, and biochemical assessment
 - FNA is critical for initial evaluation of thyroid nodule
 - Hypoparathyroidism and recurrent laryngeal nerve damage may result from surgery
- Surgical approaches
 - Lobectomy treatment of choice

Prognosis

- Excellent long-term prognosis
- Outcome indistinguishable among variants of adenoma, including oncocytic/oxyphilic variant

IMAGING

Radiographic Findings

- Imaging studies cannot reliably separate benign from malignant neoplasms
- Best study is ultrasound

Ultrasonographic Findings

- Identifies single or multiple nodules, separating adenoma from adenomatoid nodules
- Solid, homogeneous mass
- Most are isoechoic, but can be hyperechoic or hypoechoic
- Thin, well-defined, smooth, peripheral, echo-poor halo represents capsule
- Color Doppler shows spoke and wheel pattern: Peripheral blood vessels extending toward center of lesion

MR Findings

- MR used frequently in evaluating recurrent tumors rather than primary method for thyroid nodules
- T1WI: Iso- or hypointense; decreased intensity suggests hemorrhage or degeneration
- T2WI: Typically hyperintense

Nuclear Medicine Findings

- PET: Potential pitfall when imaging, since thyroid normally takes up FDG
- Thyroid scintigraphic studies: Tc-99m pertechnetate or ¹²³I
 - Most are cold nodules (absent activity)

MACROSCOPIC

General Features

- Solitary tumor, well delineated from adjacent parenchyma
- Round to ovoid
- Light, whitish-gray to tan-brown tumors, depending on cellularity and histologic type
- Rubbery, fleshy, and homogeneous solid cut surface
- Secondary changes can be seen
 - Cyst formation, infarction, fibrosis, hemorrhage, and calcification

Sections to Be Submitted

- Entire peripheral zone (parenchyma to capsule to tumor interface), unless nodule is large
- Sections perpendicular to capsule

Size

- Usually palpable if > 1 cm, but most are < 4 cm
- Currently, 1-3 cm is common
 - Improved radiographic techniques and clinical surveillance help identify smaller lesions

MICROSCOPIC**Histologic Features**

- Encapsulated tumor surrounded by variably thick fibrous connective tissue capsule
 - If capsule is thick, exclude carcinoma with additional sections or levels
- Smooth muscle-walled vessels in fibrosis help to confirm presence of true capsule
- Reticulin and elastic fibers in fibrosis also confirm capsule
- Entrapped follicular epithelium can be seen
- Tumor architecture and cytologic appearance distinct from surrounding parenchyma
- Variable architecture
 - Solid (embryonal), trabecular, microfollicular (fetal), normofollicular, macrofollicular, insular, and papillary patterns
 - 1 pattern typically dominates
- Colloid usually present, to variable degree, within follicle lumen
 - May undergo calcification, resembling psammoma bodies, especially oncocytic tumors
- Variable cellularity
- Cuboidal to polygonal cells with ample cytoplasm
- Cell borders are easily identified
- Nuclei are basal (polarized), evenly spaced, round to oval, with coarse nuclear chromatin distribution
- Nucleoli tend to be small and eccentric
- Isolated bizarre, hyperchromatic nuclei are occasionally present
- Cytoplasm ranges from cleared, eosinophilic, amphophilic, to oncocytic
 - Oncocytic type due to accumulation of abnormal mitochondria in cytoplasm
- Mitotic figures are uncommon (**except** in post-FNA setting)
- Delicate capillaries are present, but intratumoral fibrosis is uncommon
- Post-FNA changes (cystic degeneration, hemorrhage, hemosiderin-laden macrophages, calcifications, fibrosis) can mimic invasion

Variants

- Oncocytic (oxyphilic, Hürthle cell, Ashkenazy)
- Hyperfunctioning (toxic, hot)
- Adenoma with papillary hyperplasia
- Adenolipoma (lipoadenoma)
- Signet ring cell
- Clear cell variant
- Lipid-rich variant
- Adenoma with bizarre nuclei
- Atypical follicular adenoma

ANCILLARY TESTS**Cytology**

- FNA is first-line in management of solitary thyroid nodule evaluation
- Bethesda System employed for reporting thyroid FNA results
- FNA cytology does **not** discriminate among adenomatoid nodule, follicular adenoma, or follicular carcinoma
 - Consider molecular testing if 2 consecutive FNAs are atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)
 - ThyGenX: 17 analytically validated molecular markers in 1 test (13 *RAS* mutations; *BRAF*, *RET/PTCH1* and *NCOA4*; *PAX8/PPARG*)
 - Each mutation/fusion can be individually or sequentially tested
- Adequacy requires 5-6 follicular epithelial groups composed of at least 10 epithelial cells per smear for valid interpretation
- Usually cellular smears with numerous microfollicular structures
- Colloid is usually sparse
- Follicular epithelial cells are arranged in small spherical aggregates surrounding colloid droplet
- Follicular epithelial cells are round to polygonal, showing slight crowding
- Round and regular nuclei with even nuclear chromatin distribution
- Oncocytic cells have more abundant, granular cytoplasm, often associated with intranuclear cytoplasmic inclusions and nuclear irregularities

Frozen Sections

- Generally useless in accurate classification of follicular lesions
- Full capsule needs to be evaluated to exclude invasion

Histochemistry

- PAS highlights colloid

Immunohistochemistry

- Positive with keratins, TTF-1, pax-8, thyroglobulin
- Oncocytic tumors must be interpreted with caution due to high background and nonspecific staining

Genetic Testing

- Activating point mutations of *RAS* genes (specifically *NRAS* and *HRAS*) are most prevalent (~ 30% of cases)
- Somatic mutations in mitochondrial DNA (mtDNA) are found in oncocytic tumors
- If *PAX8/PPARG* rearrangement is detected, submit additional sections and perform levels, as vascular or capsular invasion can usually be identified
- Numerical chromosome changes, usually gains of chromosome 7, although 12 and 5 may be gained
 - Chromosome 7 gains seen in ~ 15% of FA (trisomy) but in ~ 45% of oncocytic adenomas (tetrasomy)

Immunohistochemistry Table

Antibody	Reactivity	Staining Pattern	Comment
Thyroglobulin	Positive	Cytoplasmic	Also seen in luminal colloid; most specific marker
TTF-1	Positive	Nuclear	
pax-8	Positive	Nuclear	All tumor cells
CK8/18/CAM5.2	Positive	Cytoplasmic	
CK-PAN	Positive	Cytoplasmic	
CK7	Positive	Cell membrane & cytoplasm	
CK19	Positive	Cell membrane & cytoplasm	Present in ~ 50% of adenomas
Calcitonin	Negative		
Chromogranin-A	Negative		
CEA-M	Negative		
Galectin-3	Equivocal		~ 10% of adenomas
HBME-1	Equivocal		~ 10% of adenomas
MSG1	Equivocal		~ 10% of adenomas

DIFFERENTIAL DIAGNOSIS

Follicular Carcinoma

- Requires identification of capsular &/or lymphovascular invasion
- Tends to have higher cellularity
- Mitotic figures are often present and increased (but < 4/10 high-power fields [HPFs])

Papillary Carcinoma, Follicular Variant

- Capsular &/or vascular invasion can be seen
- Intratumoral fibrosis helpful
- Thick, eosinophilic colloid, often with giant cells, crystalloids, and scalloping within colloid
- Large tumor cells with high nuclear:cytoplasmic ratio
- Loss of polarity or organization (misplaced around follicle)
- Nuclear irregularities, nuclear grooves, nuclear overlapping, intranuclear cytoplasmic inclusions, nuclear chromatin clearing
 - Often seen in separate foci within single tumor

Medullary Carcinoma

- Invasive growth in tumor lacking colloid
- Plasmacytoid to spindled tumor cells
- Cytoplasm is slightly granular and basophilic to amphophilic
- Salt and pepper nuclear chromatin distribution
- Many variants may overlap with adenoma
- Calcitonin, CEA, chromogranin, synaptophysin, and TTF-1 immunoreactivity

Adenomatoid (Hyperplastic) Nodule

- Usually multiple nodules lacking true capsule (although fibrosis is seen) and lacking compression of surrounding thyroid parenchyma
- Variable growth patterns within nodule(s) with abundant colloid
- Degenerative changes: Cyst formation, hemosiderin-laden macrophages, blood, fibrosis, calcification, cholesterol clefts

Parathyroid Adenoma

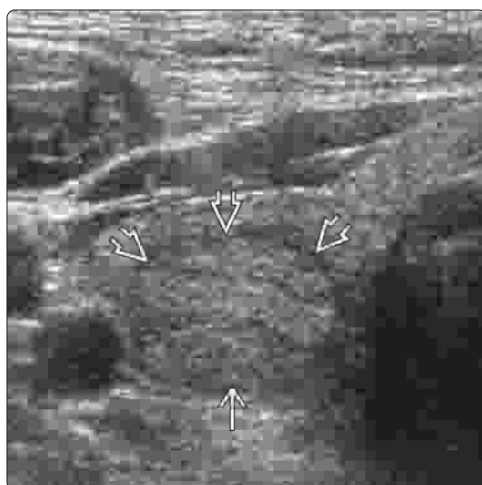
- Cell borders tend to be more prominent with clear and well-defined cytoplasm
- Nuclear chromatin is more coarse
- Parathyroid hormone and chromogranin positive, but TTF-1 and thyroglobulin negative

SELECTED REFERENCES

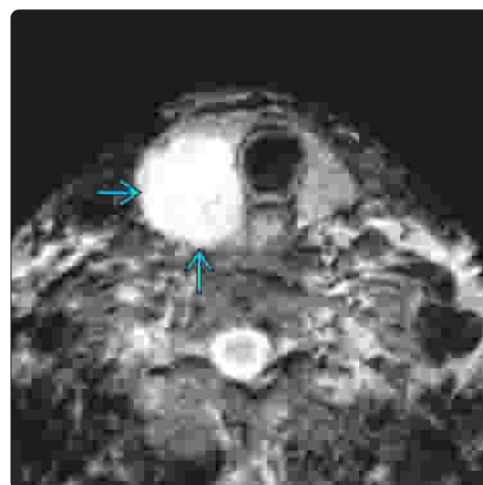
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Ultrasound: Follicular Neoplasm

(Left) Transverse ultrasound shows an isoechoic intrathyroidal mass with echo-poor periphery. The thin, well-defined, smooth, peripheral, echo-poor halo represents the capsule of this follicular adenoma. (Right) T2WI MR shows a uniformly hyperintense mass within the right lobe of the thyroid. The mass appears well defined and does not extend beyond the thyroid gland. There is no neck adenopathy present. While not diagnostic, the MR appearance suggests a benign diagnosis.

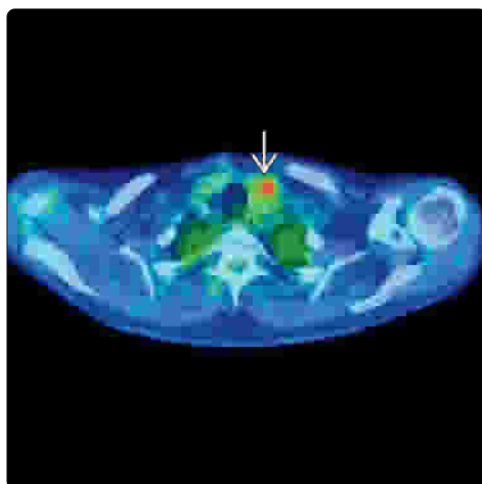


T2 MR: Follicular Adenoma



PET With Increased Activity

(Left) PET scan using FDG shows an avid thyroid nodule. This finding confirms a mass but does not give a diagnosis (which proved to be adenoma in this case). PET scans frequently show thyroid uptake, but a single mass with more avid uptake requires further evaluation. (Right) There is a thick, well-formed fibrous connective tissue capsule separating a neoplasm from the surrounding parenchyma. There is compression of the adjacent thyroid, which is more beefy red than the tumor.

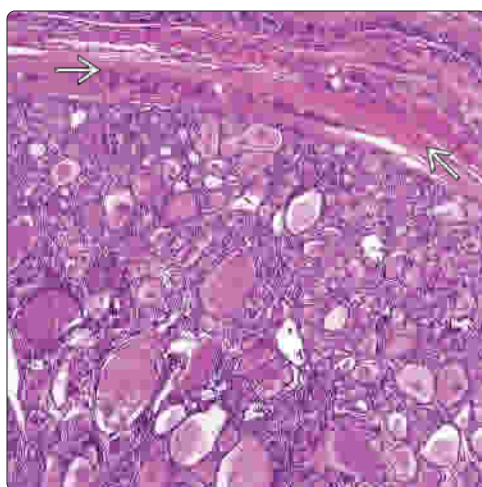


Gross of Follicular Adenoma

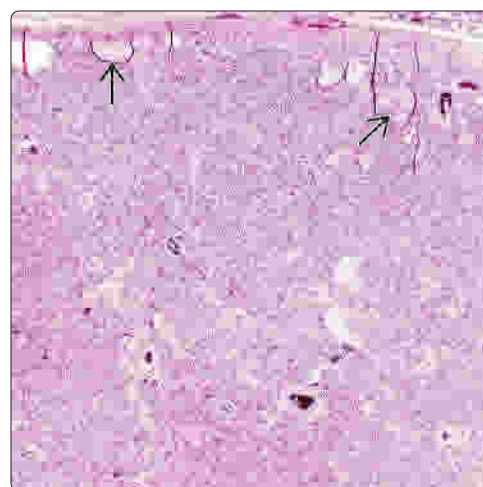


Thin Capsule

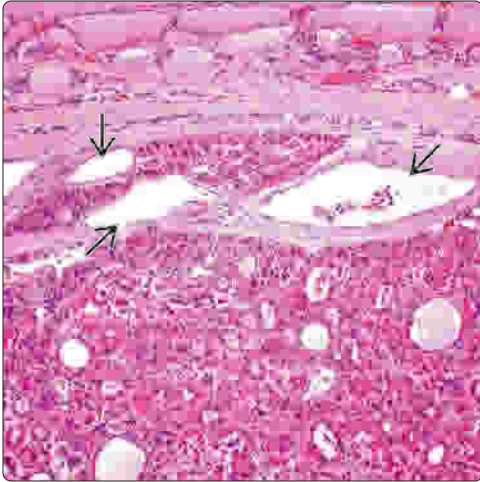
(Left) There is a thin fibrous connective tissue capsule surrounding a tumor whose appearance is distinct from the adjacent, compressed thyroid parenchyma. Colloid is easily identified within the follicles. This is a characteristic low-power finding of follicular adenoma. (Right) A thin but easily identified capsule surrounds this follicular adenoma. Colloid is present but is not seen throughout. Adenomas can be quite cellular, as shown in this example.



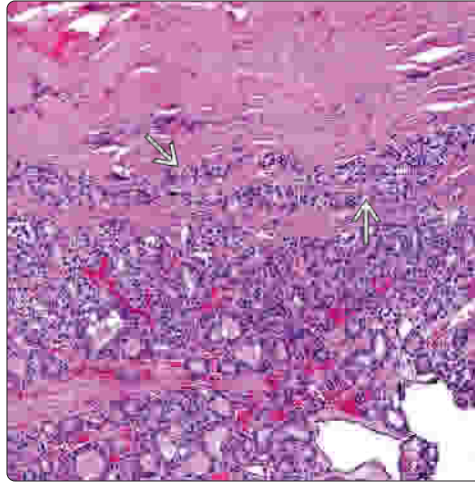
Cellular Follicular Adenoma



Penetrating Vessels With Entrapment

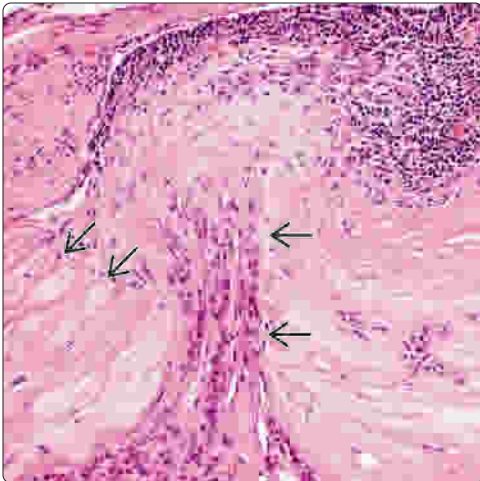


Entrapped Follicular Epithelium

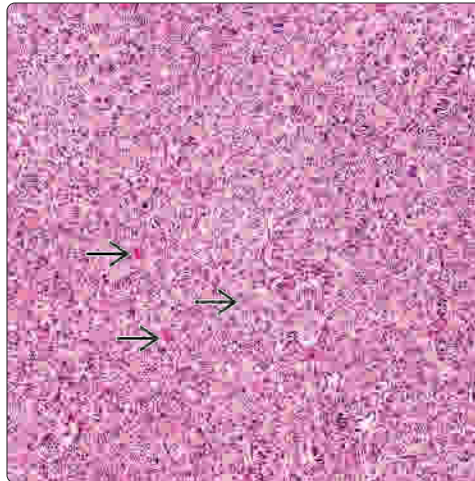


(Left) The capsule is slightly irregular. Note the subcapsular vessels [X], which have entrapped part of the oncocyctic neoplastic cells between them. This does not represent vascular or capsular invasion in this follicular adenoma. (Right) Follicular neoplasms will frequently have new collagen deposition. New collagen frequently entraps the neoplastic cells [X], but this does not represent invasion. The collagen often blends with the tumor cells. Careful review of these areas is required to render the correct diagnosis.

Fine-Needle Aspiration Tract

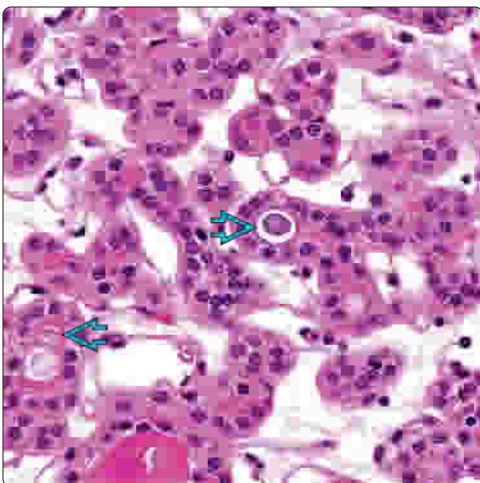


Trabecular to Insular Architecture

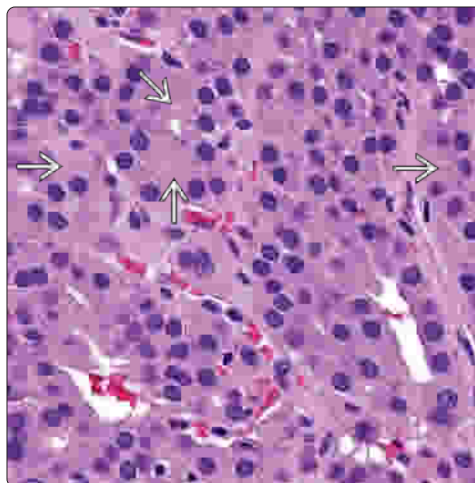


(Left) A FNA tract can simulate invasion. However, there is an abrupt cut [X] within the capsule (caused by sharp needle point), associated with lymphocytes, extravasated erythrocytes, and reactive myxoid stroma. Tumor cells frequently stream through the hole. (Right) Follicular adenomas are usually quite cellular. Colloid is identified [X], although not abundant. The tumor has a vaguely trabecular or insular architecture.

Calcified Colloid




Follicular Adenoma

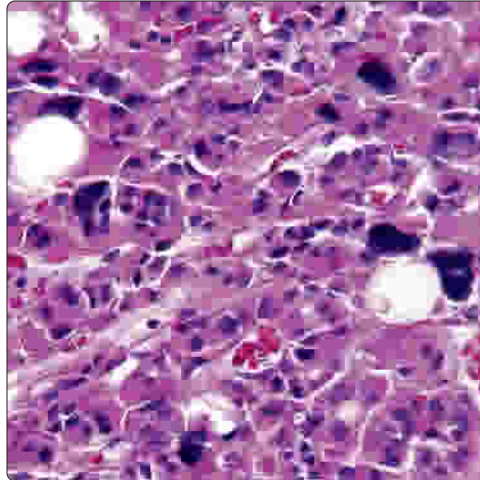


(Left) Sometimes adenoma will have edematous stroma, creating a pseudopapillary appearance. Note that the colloid is focally showing early calcification [X] within the follicles. (Right) Hematoxylin & eosin shows granular, opacified cytoplasm. This is on the spectrum of oxyphilia but does not change the diagnosis. Colloid is often difficult to identify [X]. Oncocytic tumor may require thyroglobulin to confirm the diagnosis.

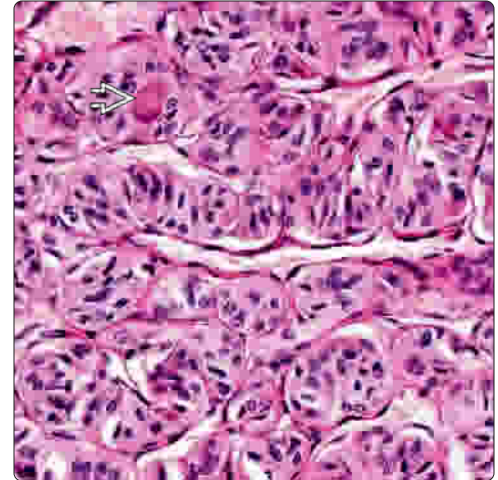
Follicular Adenoma

Pleomorphism in Follicular Adenoma

(Left) There is remarkable pleomorphism visible in this section, which can also be seen in many endocrine organ tumors. Note the cytoplasm is oncocytic (oxyphilic, Hürthle) in these neoplastic cells. Pleomorphism is more frequent in oncocytic neoplasms. (Right) A variety of different patterns can be seen in follicular adenoma. This is a trabecular pattern. Note the well-formed trabeculae, separated by a delicate fibrovascular stroma. Colloid is present . The nuclei are round-oval, with coarse chromatin distribution.

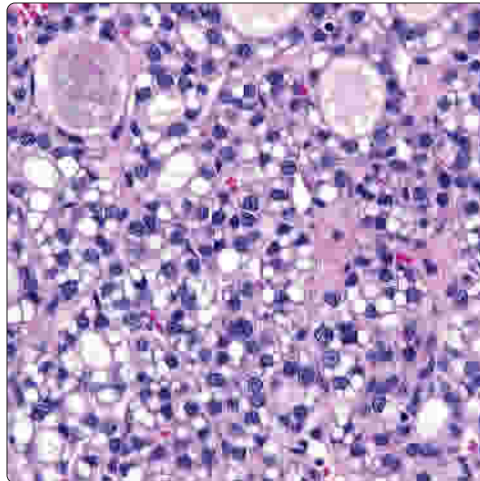


Trabecular Pattern

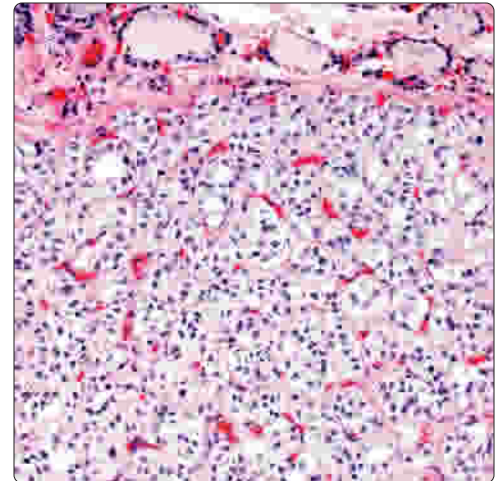


Signet Ring Features


(Left) This field shows a signet ring morphology, a finding seen in only a few follicular adenomas. Thyroglobulin can be used to highlight the signet ring spaces. (Right) A slightly cleared cytoplasm can be seen in follicular adenomas, as well as in other thyroid tumors. This tumor also has a vague paraganglioma-like growth pattern. Variant adenoma types may require ancillary techniques to confirm the diagnosis. The cells would be thyroglobulin and TTF-1 positive.

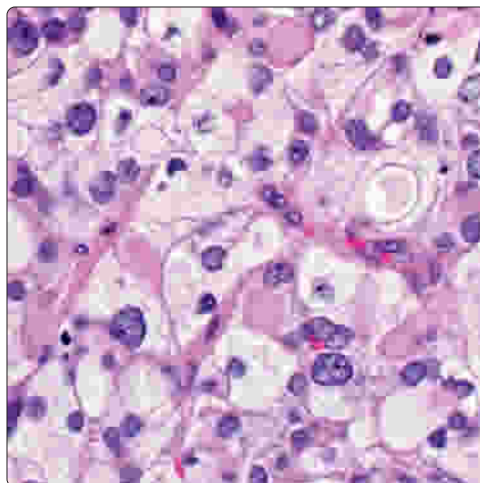


Paraganglioma-Like Pattern

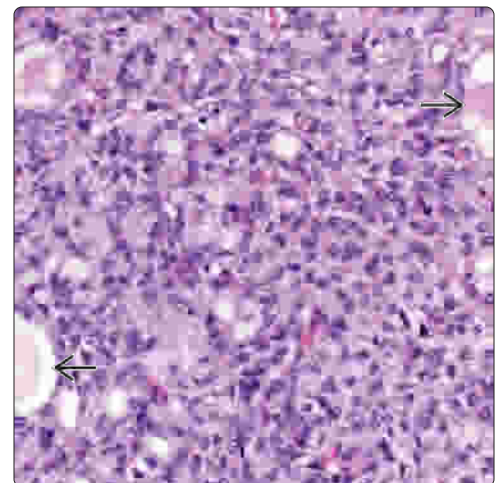


Lipid-Rich Variant

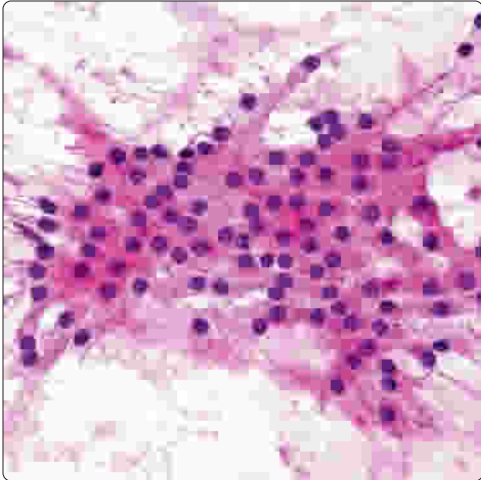
(Left) The lipid-rich variant will show abundant microvesicular cytoplasm surrounding slightly irregular nuclei. Colloid is still easily identified throughout. (Right) The spindle cell variant shows a spindled tumor cell population making up the majority of the neoplasm. However, colloid  is still present. The cells would be positive with thyroglobulin, pax-8, and TTF1.



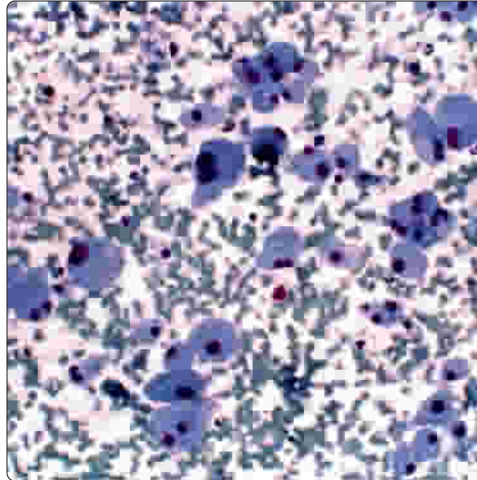
Spindle Cell Adenoma



Sheet of Follicular Epithelium

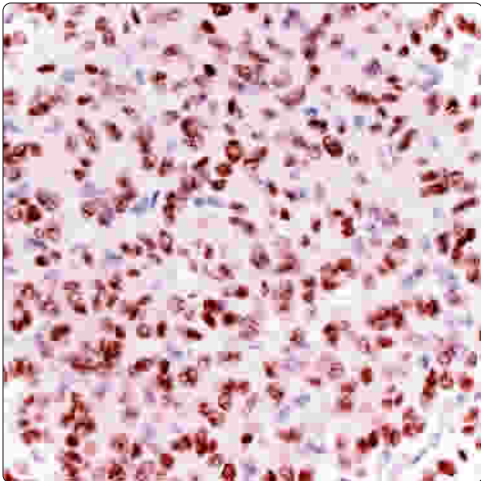


Oncocytic Follicular Cells

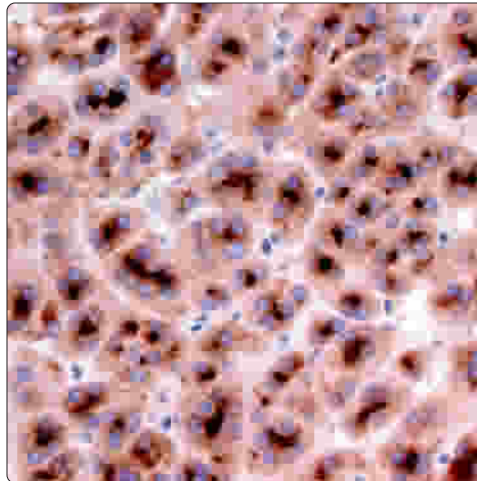


(Left) There is a sheet of follicular epithelial cells arranged in a vague follicular appearance. The cytoplasm is abundant and granular or eosinophilic. The nuclei are round and regular with even chromatin distribution. (Right) Single cells or small clusters can be seen in a follicular neoplasm. There is no colloid present in the background of this image. The cells are large with abundant, granular cytoplasm. The nuclei are dark and round. These changes can be seen in an adenoma.

TTF-1 Reaction in Spindle Cell Variant

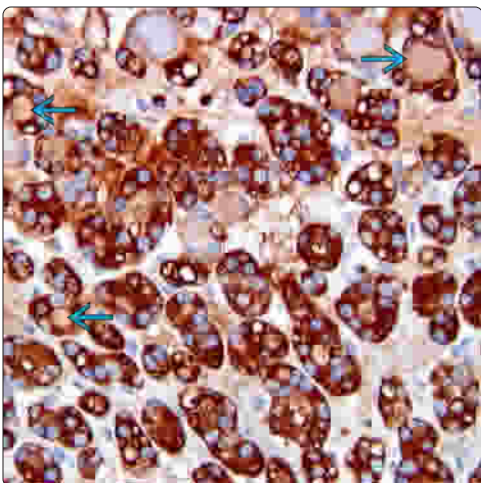


Thyroglobulin Reaction

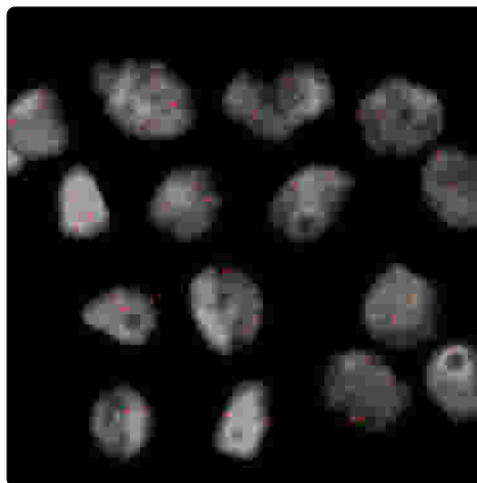


(Left) Cellular tumors frequently show an absence of colloid. Sometimes TTF-1 can be used to highlight the nuclei of the neoplastic cells, as it does in this spindle cell variant. This reaction does not separate benign from malignant lesions, although it may confirm thyroid origin. (Right) Oncocytic tumors especially may have very limited colloid. Thyroglobulin can be used to highlight the small globules of thyroglobulin both within the cytoplasm and within the follicular spaces.

Signet Ring Thyroglobulin Reaction



FISH Chromosome Evaluation



(Left) This is an example of thyroglobulin staining in a signet ring-type of follicular adenoma. Note the strong and heavy cytoplasmic reaction, while the background colloid stains less avidly. (Right) FISH with a chromosome 7 centromeric probe highlights 3 copies of chromosome 7 (red dots within each nucleus). This is the most common chromosomal gain (trisomy 7) seen in adenoma.

Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclei

KEY FACTS

TERMINOLOGY

- **Noninvasive**, partially to completely encapsulated thyroid follicular neoplasm arranged in almost exclusively follicular architecture, showing papillary carcinoma-like nuclear features in adequately sampled tumor

CLINICAL ISSUES

- Overall, ~ 20% of all thyroid gland neoplasms
- Mean: 46 years; range: 20-80 years
- Females > males (4:1)
- Most (~ 60%) are unicentric
- Lobectomy alone without radioablative iodine yields excellent long-term clinical outcome

MACROSCOPIC

- Circumscribed, usually encapsulated 3 cm (mean) tumors

MICROSCOPIC

- By definition, there must be no capsular or angioinvasive/lymphatic invasion



- Follicular pattern: Small, tight, well-formed follicles
- < 1% papillary structures
- Abundant, hypereosinophilic colloid, often scalloped
- Intratumor fibrosis usually present
- Nuclear features of papillary carcinoma are present, but not uniformly
- **Nuclear features** include
 - Size and shape: Nuclear enlargement, crowding, overlapping, with elongation to ovoid nuclei
- Membrane irregularities: Irregular contours, grooves, folds
- Nuclear chromatin: Cleared, even, fine to delicate with margination; nucleoli on nuclear membranes

ANCILLARY TESTS

- Most common: *RAS* mutations

TOP DIFFERENTIAL DIAGNOSES

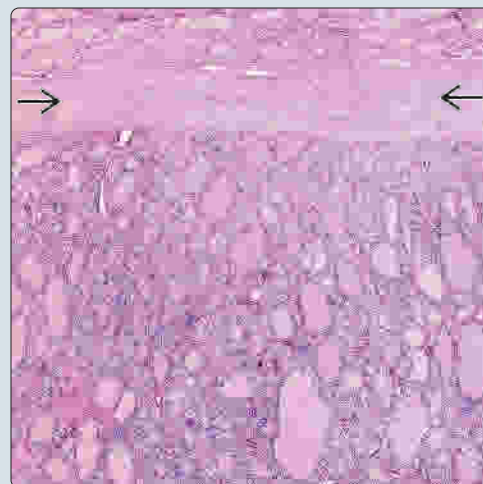
- Follicular adenoma, papillary thyroid carcinoma (classical and invasive follicular variant), follicular thyroid carcinoma

(Left) There is an easily identified capsule  surrounding this follicular neoplasm, lacking any capsular or angioinvasive/lymphatic invasion. (Right) Most of these neoplasms show a very thick and well-formed fibrous connective tissue capsule  surrounding the neoplastic proliferation of follicular cells. Colloid is easily identified.

Noninvasive Encapsulated Neoplasm

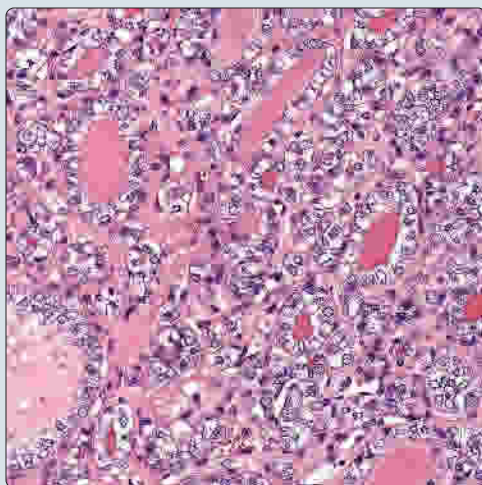


Thick Fibrous Connective Tissue Capsule

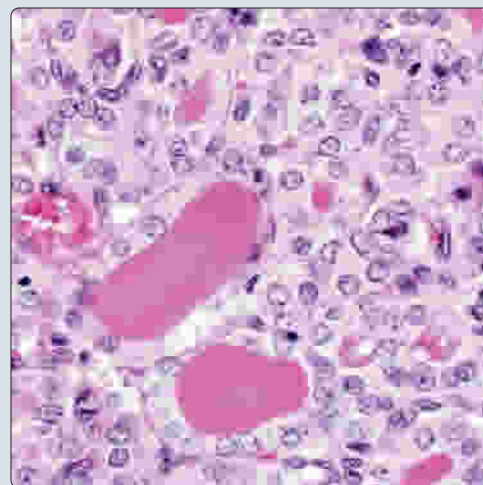


(Left) The classical papillary thyroid carcinoma nuclear features are seen in this example of noninvasive follicular thyroid neoplasm with papillary-like nuclei (NIFTP). There is nuclear enlargement, overlapping and nuclear chromatin clearing. Hypereosinophilic colloid is seen. (Right) There is hypereosinophilic colloid within the follicles, which are lined by atypical nuclei, showing nuclear enlargement, contour irregularities, and grooves. Nuclear chromatin clearing is seen.

Papillary Nuclear Features



Nuclear Enlargement



TERMINOLOGY

Abbreviations

- Noninvasive follicular thyroid neoplasm with papillary-like nuclei (NIFTP)

Synonyms

- Papillary thyroid carcinoma (PTC), follicular variant, encapsulated type
- Encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC)

Definitions

- **Noninvasive**, partially to completely encapsulated thyroid follicular neoplasm arranged in almost exclusively follicular architecture, showing papillary carcinoma-like nuclear features in adequately sampled tumor
- **Specific exclusions to this category**
 - No invasion; no solid, trabecular, or insular architecture; > 1% papillary structures; tumor necrosis; ≥ 4 mitoses/10 HPF

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Environmental or therapeutic radiation exposure

CLINICAL ISSUES

Epidemiology

- Incidence
 - 25-30% of papillary carcinomas fall into follicular variant category
 - Overall, ~ 20% of all thyroid gland neoplasms
 - Difficult to estimate as newly recognized category
- Age
 - Range: 20-80 years
 - Mean: 46 years
- Sex
 - Females > males (4:1)

Site

- Most (~ 60%) are unicentric, ~ 25% are multicentric (1 lobe), and 15% are bilateral
- Any lobe or isthmus may be affected

Presentation

- Slowly growing thyroid gland/lobe mass
- Tumors are often present for long duration

Treatment

- Lobectomy alone is appropriate therapy
- Occasionally, thyroidectomy is performed for other reasons but is not required
- Postoperative radioablative iodine is not recommended
- Lymph node dissection is not recommended

Prognosis

- Excellent long-term clinical outcome
 - No recurrence or biochemical evidence of disease with median follow-up of > 10 years
- Virtually no tumor recurrence, lymph node or distant metastasis

- Cases with metastases or recurrence usually do not fulfill inclusion/exclusion criteria
 - i.e., showed invasion; were not well sampled, showed necrosis, contained papillae, were solid, etc.

IMAGING

General Features

- Single, encapsulated mass on ultrasound, computed tomography, &/or MR
- Cold on scintigraphic studies, although not usually performed

MACROSCOPIC

General Features

- Circumscribed, usually well-encapsulated tumors, with distinctly different appearance from adjacent parenchyma
- Lacks invasion
- Colloid is easily identified
- **No** papillary structures or tumor necrosis

Size

- Range: 0.5 cm to 10 cm
- Mean: ~ 3 cm
- Tend to be larger than classical papillary carcinoma cases

Sections to Be Submitted

- Ideally, entire tumor-capsule-parenchyma interface should be sampled to exclude invasion
- Practically, if 3 sections per cm of tumor are submitted, often with several sections per cassette, followed by additional sections if review shows any questionable areas

MICROSCOPIC

Histologic Features

- **Capsule**
 - Well formed in majority of cases
 - May be partially circumferential or attenuated, incomplete encapsulation
 - Contains smooth muscle-walled vessels in fibrous connective tissue
- **Noninvasive**
 - By definition, there must be **no** capsular or angioinvasive/lymphatic invasion
 - Must be well sampled for this criterion to be met
- **Architecture**
 - Follicular pattern
 - Small, tight, well-formed follicles
 - Variable cellularity: Hypercellular foci in multiple sites within tumor nodule
 - Papillae must be absent or isolated, rudimentary papillary structures
 - < 1% of tumor volume can show papillary structures and still be included in this tumor category
 - Evaluate hypercellular areas for nuclear features
- **Colloid**
 - Abundant, easily identified colloid, often with scalloping
 - Hypereosinophilic colloid within follicles
 - May contain histiocytic giant cells
 - Crystalloids (rhomboid or needle-shaped) may be seen

Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclei

- **Intratumor fibrosis usually present**
 - Intratumoral, acellular, eosinophilic fibrosis interspersed between follicles
- **Cytology**
 - Flattened to cuboidal to columnar cells
 - Increased nuclear:cytoplasmic ratio
 - Enlarged cells compared to adjacent, uninvolved parenchyma
 - Nuclear features of papillary carcinoma are present, but not uniformly
 - Patchy, but multifocal, often at periphery of tumor nodule
 - ≥ 3 HPF within 3 mm linear area of tumor (diameter) is good rule of thumb to apply
 - **Nuclear features** include
 - Size and shape
 - Nuclear enlargement, crowding, overlapping
 - Loss of polarity, elongation, ovoid nuclei
 - Membrane irregularities
 - Irregular contours, grooves or folds, pseudo-inclusions
 - Nuclear chromatin
 - Clearing, nuclear margination, and even, fine, delicate nuclear chromatin
 - Nucleoli on nuclear membranes
 - Scoring system: 1 point for each nuclear feature present, with total score of 2-3, placing tumor in this category
 - 98.6% sensitivity; 90.1% specificity; 94.3% classification accuracy
- **Exclusions**
 - $> 1\%$ papillae; solid, insular, organoid, or trabecular growth; tumor necrosis; ≥ 4 mitoses per 10 HPF

ANCILLARY TESTS

Cytology

- Difficult to diagnose prospectively
- Usually classified as Bethesda group II, III, or IV
- Cellular smears with follicular structures and 3-D groups
- Round to elongated nuclei in syncytium, with rare grooves and folds
- Delicate, fine to even nuclear chromatin distribution
- Scant, bubble gum-like colloid

Frozen Sections

- Often called "follicular neoplasm, defer to permanent"
- Touch preparation &/or smears may help identify papillary nuclear features
- Cannot adequately assess periphery to exclude invasion, and thus frozen section is not useful

Immunohistochemistry

- Various immunohistochemistry findings similar to PTC
 - HBME-1, galectin-3, MSF1 (CITED-1)

Genetic Testing

- Most common: *RAS* mutations
 - *NRAS* mutation in codon 61 is most common
- *THADA* and *PAX8/PPARG* gene fusions are seen less often
- Generally, *BRAFV600E*, *RET/PTCH1* or *NCOA4*, and *TERT* are not identified in this tumor

DIFFERENTIAL DIAGNOSIS

Follicular Adenoma

- Noninvasive follicular pattern neoplasm with colloid production
- Absent nuclear features of papillary carcinoma
- Frequently shows *RAS* mutations

Papillary Thyroid Carcinoma, Follicular Variant

- Identical architecture and cytologic features, with invasion
- Capsular &/or angioinvasive/lymphatic invasion must be documented to place in this category

Papillary Thyroid Carcinoma, Classical Type

- Sclerotic, infiltrative periphery, usually capsule can be seen
- Demonstrates dominant papillary architecture
- Classical nuclear features of papillary thyroid carcinoma
- Usually *BRAF* or *RET/PTCH1* or *NCOA4*, among other mutations

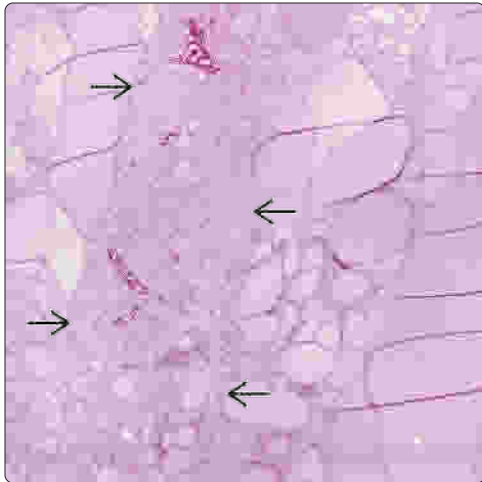
Follicular Thyroid Carcinoma

- Encapsulated follicular neoplasm arranged in follicular to solid pattern with colloid production
- Invasion must be documented
 - Capsular &/or angioinvasive/lymphatic invasion present
- Lacks nuclear features of papillary carcinoma

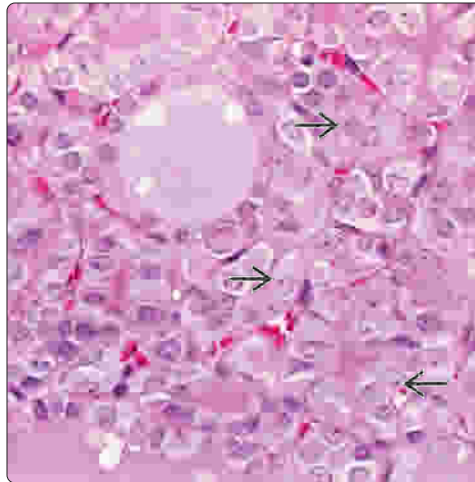
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Hypercellular Foci

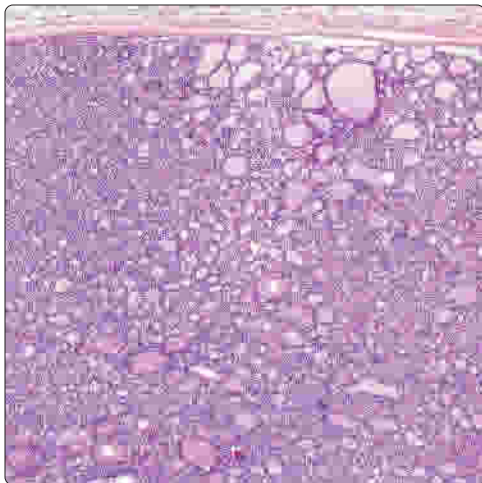


Powdery Nuclear Chromatin

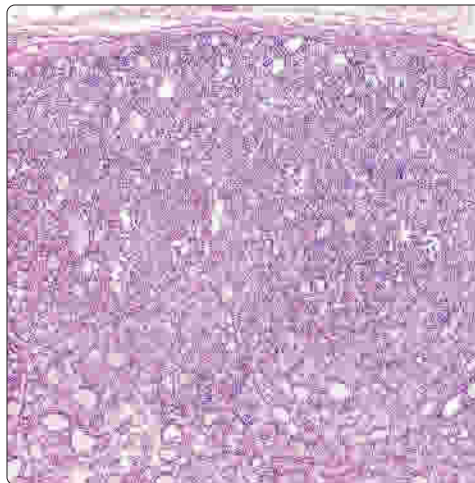


(Left) The histologic features are not uniformly present in the tumor nodule. This hypercellular area [box] would be the region to examine on high power to confirm papillary nuclear features. **(Right)** The enlarged nuclei show delicate, powdery, fine nuclear chromatin distribution, with isolated nuclear grooves. There are small nucleoli, preferentially at the nuclear membrane [box].

Thin Capsule Around Cellular Tumor

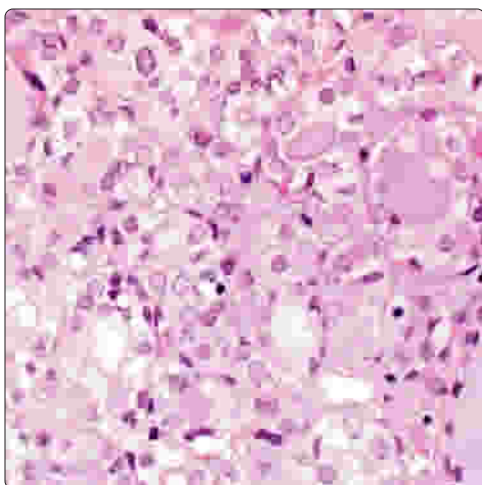


Thin Capsule

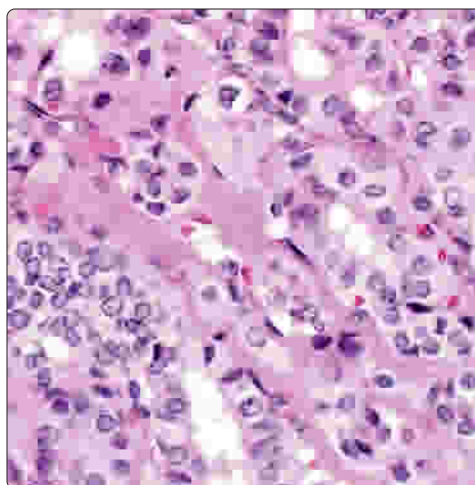


(Left) There is a thin but well-formed fibrous connective tissue capsule surrounding this follicular-patterned neoplasm. Note the easily identified colloid throughout and a lack of papillary structures. **(Right)** There is a very thin but intact fibrous connective tissue capsule lacking invasion. The follicular architecture is easily identified throughout the neoplasm.

Irregular Nuclei



Intratumoral Fibrosis



(Left) There is hypereosinophilic colloid in the follicles, which are lined by atypical nuclei. There is delicate nuclear chromatin, contour irregularities, nuclear grooves, and small nucleoli on the nuclear membranes. **(Right)** There are bands of acellular, eosinophilic fibrous connective tissue within the tumor, separating the follicles. Note the nuclear enlargement, irregular placement, overlapping, and contour irregularities.

Hyalinizing Trabecular Tumor

KEY FACTS

TERMINOLOGY

- Rare tumor of follicular cell origin with trabecular pattern of growth and marked intratrabecular hyalinization

CLINICAL ISSUES

- Very rare primary tumor type
- Mean age: 50 years
- Female >>> male (6:1)
- Nearly all are benign with excellent long-term prognosis after excision

MACROSCOPIC

- Solitary, solid, encapsulated or well-circumscribed yellow-tan tumor
- Cut surface is solid, homogeneous, lobulated
- Mean size: 2.5 cm; range: 0.3-7.0 cm

MICROSCOPIC

- Cellular tumors arranged in trabecular pattern

- Polygonal to fusiform cells, with oval-elongated nuclei
- Nuclei arranged perpendicular to trabeculae long axis
- Nuclear grooves, intranuclear pseudoinclusions, perinucleolar halos
- Distinctive, paranuclear, cytoplasmic yellow bodies
- Tumor nests formed by intratrabecular dense, heavily hyalinized eosinophilic fibrovascular stroma
- Calcospherites may be present


ANCILLARY TESTS

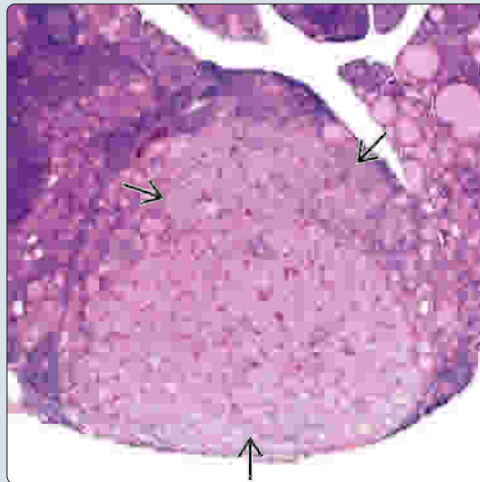
- **Positive:** Thyroglobulin, TTF-1, pancytokeratin, CK7, Ki-67 (MIB-1 monoclonal) **membrane** staining

TOP DIFFERENTIAL DIAGNOSES

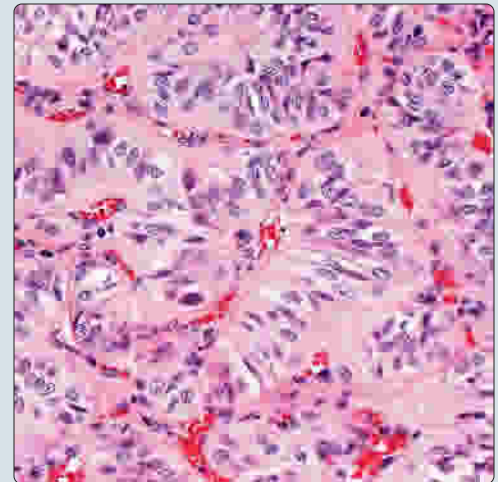
- Papillary carcinoma
- Follicular adenoma and follicular carcinoma
- Medullary thyroid carcinoma
- Paraganglioma

Well-Defined, Circumscribed Tumor



(Left) Hematoxylin & eosin shows a low-power view of a well-defined, although in this case, unencapsulated tumor . The tumor cells appear to be arranged in a trabecular fashion even at this low power. The remaining thyroid gland shows lymphocytic thyroiditis. (Right) Hematoxylin & eosin at high power demonstrates the spindle, fusiform cells with oval-shaped nuclei containing multiple nuclear grooves. Note the perpendicular arrangement of the nuclei to the axis of the trabeculae.

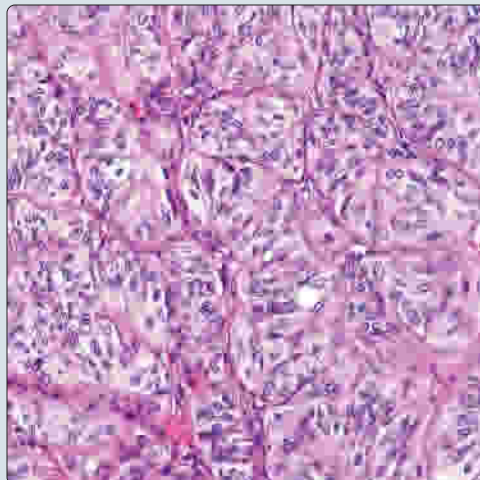


Perpendicular Spindled Tumor Cells

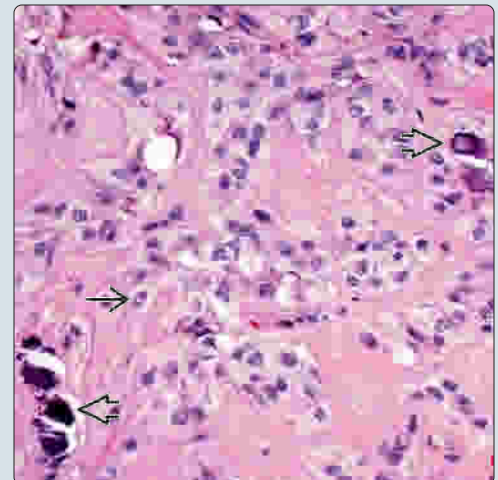


Trabecular Architecture

(Left) Hematoxylin & eosin shows the trabecular architecture composed by cells arranged perpendicular to the axis of the trabeculae. The cells are spindled to fusiform. (Right) Trabecular growth shows hyalinization within and between the trabeculae and nests. Irregular nuclei with intranuclear cytoplasmic inclusions  are present. There are isolated calcifications . Colloid is not present in this field.



Marked Hyalinization and Calcifications



TERMINOLOGY

Abbreviations

- Hyalinizing trabecular tumor (HTT)

Synonyms

- Hyalinizing trabecular adenoma (HTA)
- Paraganglioma-like adenoma of thyroid (PLAT)

Definitions

- Rare tumor of follicular cell origin with trabecular pattern of growth and marked intratrabecular hyalinization
- Exceedingly rare, tumors show capsular or vascular invasion

ETIOLOGY/PATHOGENESIS

Radiation

- Several cases have occurred following radiation exposure

Related to Papillary Carcinoma

- Nuclear features suggest relationship to papillary carcinoma
- *RET/PTC* rearrangement in a few tumors suggests this relationship

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very rare primary tumor type
 - < 1% of all primary thyroid gland neoplasms
- Age
 - Mean: 50 years; seldom < 30 years
- Sex
 - Female > > male (6:1)

Presentation

- Usually asymptomatic and incidentally found during routine physical exam
- Palpable, solitary mass in rare cases
- May be found incidentally in multinodular glands removed for different reason
- Typically euthyroid
- Rare association with radiation

Treatment

- Complete but conservative excision
 - Lobectomy is sufficient (although thyroidectomy may have been performed for different reason)

Prognosis

- Nearly all are benign with excellent long-term prognosis
- Isolated cases have developed lymph node metastases
 - Metastases develop in patients with tumors that show invasion (capsular or vascular)
 - Metastasis suggests possible relationship with papillary carcinoma
 - In review of 112 patients, only 1 developed pulmonary metastases (tumor showed invasion)

IMAGING

Radiographic Findings

- US shows solid nodule, with hypoechoic or heterogeneous echogenicity
 - High intratumoral blood flow on color Doppler

MACROSCOPIC

General Features

- Solitary, solid, encapsulated or well-circumscribed tumor
- Cut surface is solid, homogeneous, delicately lobulated
- Yellow-tan or light tan with flecks and streaks
- Patulous vessels and calcifications are rare

Size

- Mean: 2.5 cm; range: 0.3-7.0 cm

MICROSCOPIC

Histologic Features

- Circumscribed with thin, irregular, and uneven fibrous connective tissue capsule
 - Vascular or capsular invasion is almost always absent
- Cellular tumors arranged in trabecular, alveolar, or insular growth
 - Straight or curvilinear bands of tumor cells 2-4 cells thick
- Scant to absent colloid
- Medium to large, polygonal to fusiform cells
- Oval to elongated nuclei arranged perpendicular to long axis of trabeculae and fibrovascular stroma
- Prominent nuclear grooves, nuclear contour irregularities, intranuclear cytoplasmic inclusions, and perinucleolar halos
- Variable cytoplasm, usually finely granular, acidophilic, amphophilic, or clear
 - Tends to have homogeneous, glassy, or more granular texture
- Distinctive, round, refractile, paranuclear, cytoplasmic yellow bodies/vacuoles (giant lysosomes), about 5 µm
 - Homogeneous or granular texture, occasionally surrounded by clear zone
- Tumor nests formed by intratrabecular dense, heavily hyalinized eosinophilic fibrovascular stroma
 - Hyalinization is usually more prominent at periphery of trabeculae
 - PAS-**positive** (diastase resistant) basement membrane material
 - May resemble amyloid but is Congo red **negative**
- Calcospherites (psammoma or calcific bodies) may be present
- Mitotic figures are uncommon

ANCILLARY TESTS

Cytology

- Smears are frequently interpreted as papillary carcinoma or medullary carcinoma
- Cellular aspirates with bloody background
- Cohesive clusters of cells with abundant cytoplasm
- Elongated nuclei with evenly dispersed chromatin and intranuclear cytoplasmic inclusions and grooves
- Lumpy stromal deposits of basement membrane material

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
TTF-1	Positive	Nuclear	Nearly all tumor cells
Thyroglobulin	Positive	Cytoplasmic	Cytoplasmic and colloid-type deposition
Ki-67	Positive	Cell membrane	Strong and diffuse, but only if using Dako MIB-1 antibody
CK-LMW-NOS	Positive	Cytoplasmic	Nearly all tumor cells
CK7	Positive	Cytoplasmic	Most tumor cells
Galectin-3	Positive	Cytoplasmic	~ 40% of tumor cells
HBME-1	Positive	Cytoplasmic	
Laminin	Positive	Stromal matrix	Hyaline material reaction
Collagen IV	Positive	Stromal matrix	Hyaline material reaction
Calcitonin	Negative		
Chromogranin-A	Negative		
S100	Negative		
CK19	Negative		

- Irregularly shaped deposits between cells
- Round, centrally located aggregates of material with radial orientation, frequently surrounding cells
- Cytoplasmic bodies (yellow bodies) are green (Papanicolaou stain) or pink (Diff-Quik stain)
- Psammoma bodies/calcifications can be seen

Histochemistry

- PAS-positive, diastase-resistant stromal matrix

Immunohistochemistry

- **Positive:** Thyroglobulin, TTF-1, pancytokeratin, CK7, Ki-67 (MIB-1 monoclonal) membrane staining
- **Negative:** Calcitonin, chromogranin, S100 protein

Genetic Testing

- *RET/PTCH1* or *NCOA4* fusion gene by RT-PCR in few tumors
- *BRAF*, *HRAS*, *NRAS*, and *KRAS* gene mutations absent

Electron Microscopy

- Nests and cords of cells surrounded by basal lamina
- Nuclei have irregular contours with multiple indentations and intranuclear grooves and pseudoinclusions
- Large, membrane-bound lysosomes, containing vacuoles, granular material, and regularly stacked membranes or fingerprint bodies
- Lumpy accumulation of basement membrane material

DIFFERENTIAL DIAGNOSIS

Papillary Carcinoma

- Extensive intratrabecular stromal hyalinization very rare in papillary carcinoma
- Invasive growth; papillary and follicular pattern suggests papillary carcinoma
- Overlapping nuclear features: Nuclear grooves, pseudoinclusions
- Psammoma bodies (not calcified intraluminal colloid)
- *BRAF* mutation confirms papillary carcinoma; *RAS* mutations excludes HTT

Follicular Adenoma/Carcinoma

- Widely invasive growth (vascular and capsular) supports follicular carcinoma
- **Intertrabecular**, perivascular stromal hyalinization can be seen in adenoma/carcinoma
- Perpendicular arrangement of nuclei, grooves, and pseudoinclusions more common in HTT

Medullary Thyroid Carcinoma

- Invasive tumor, often with multiple growth patterns
- Lack of colloid common to both
- Amyloid can mimic hyalinization, but will be Congo red **positive**
- **Positive:** Calcitonin, chromogranin, CEA; **negative:** Thyroglobulin

Paraganglioma

- Histology alone may overlap extensively, although hyalinization not usually seen
- **Positive:** Chromogranin, synaptophysin, CD56, S100 protein (sustentacular)

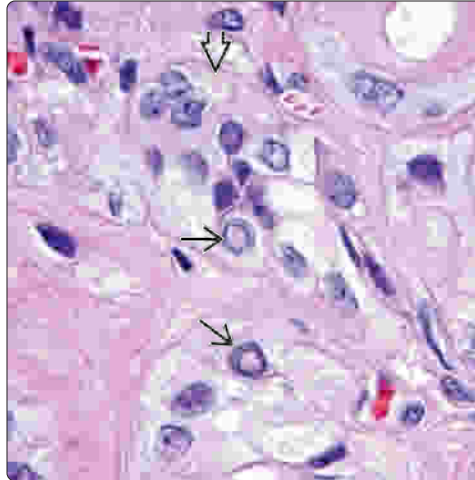
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Well-Circumscribed Tumor

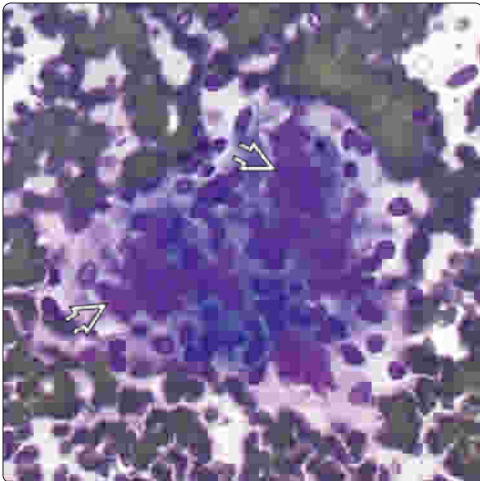


Intranuclear Inclusions and Yellow Bodies

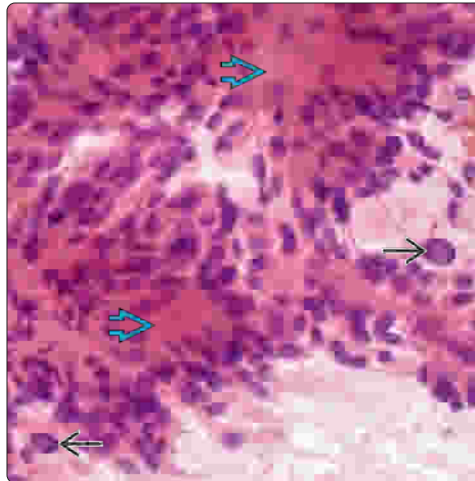


(Left) Well-circumscribed tumor shows a homogeneous, slightly lobulated, solid cut surface, yellow to tan in appearance. There are several patulous vessels. (Right) There is well-developed hyalinization between the nests of tumor cells. Intranuclear cytoplasmic inclusions [E] are a common finding in hyalinizing trabecular tumor (HTT). Cytoplasmic yellow bodies are unique to this tumor [E].

Hyaline Material Between Follicular Cells

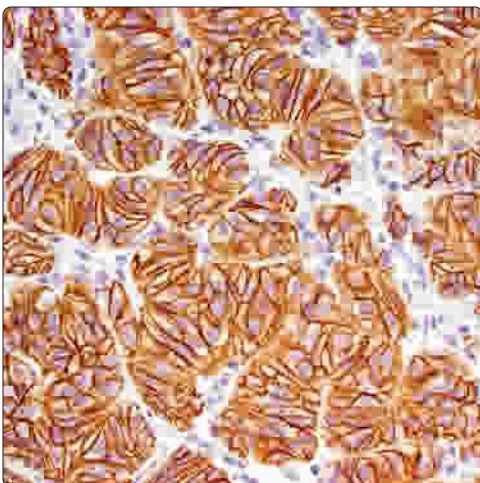


Hyaline Material and Nuclear Inclusions

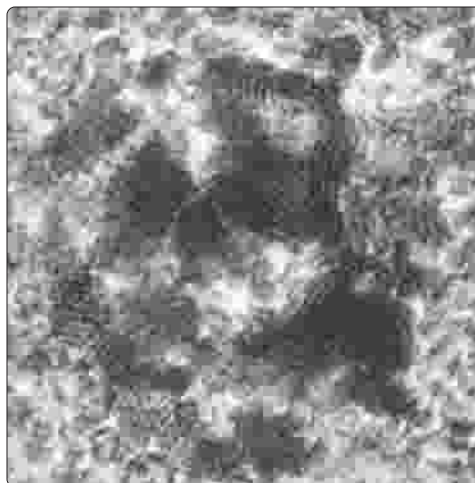


(Left) Diff-Quik stained material shows clusters of neoplastic cells immediately associated with aggregates of dense pink hyaline material [E]. This material is the "hyalinization" characteristic for the name of the tumor. (Right) PAP-stained material shows sheets of neoplastic cells surrounding aggregates of hyaline material [E], much paler on alcohol-fixed preparations. Intranuclear cytoplasmic inclusions are noted in the elongated nuclei with evenly dispersed chromatin [E].

Membrane Staining With Ki-67



Fingerprint Bodies Represent Yellow Bodies



(Left) Ki-67 yields a very strong and characteristic membrane and peripheral cytoplasmic reactivity. The membranous staining is only identified with the Dako MIB-1 antibody (epitope retrieval independent) and not with other antibodies. (Right) The yellow body seen by light microscopy, by EM, is probably a giant lysosome, containing regularly stacked membranes that form fingerprint bodies, which are quite characteristic for this particular thyroid gland tumor type.

Thyroid Teratoma

KEY FACTS

TERMINOLOGY

- Tumor of germ cell derivation composed of mature or immature tissues derived from all 3 germ cell layers: Ectoderm, mesoderm, and endoderm

CLINICAL ISSUES

- Bimodal age distribution
 - Neonates and infants: Nearly all are benign or immature teratomas (grade 0, 1, or 2)
 - Children and adults: Preponderance of malignant teratomas (grade 3)
- All patients present with neck mass
- Outcome depends on patient's age, tumor size, and presence and proportion of immaturity
- Surgery must be instituted immediately in neonatal cases to avoid morbidity or mortality

MACROSCOPIC

- Tumor surface is smooth to bosselated or lobulated

- Firm to soft and multilocular-cystic
- Gray-tan or yellow-white to translucent cut surface

MICROSCOPIC

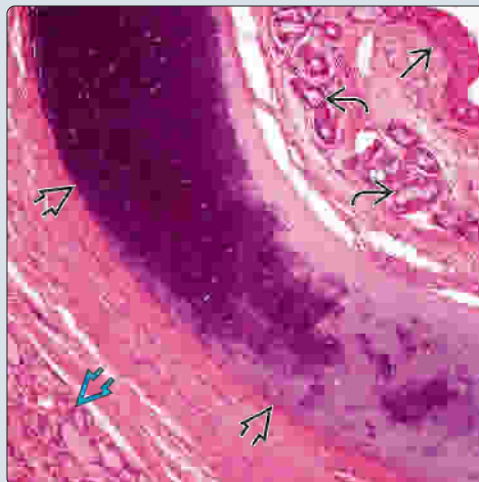
- Tissues from all 3 primordial layers
- By definition, thyroid parenchyma must be present
- Wide array of tissue types and growth patterns
- Variety of different epithelia, neural tissue (most common), and mesenchymal elements
- Maturation and relative proportions of immature neuroectodermal tissue determines grade
 - Completely mature (grade 0)
 - Predominantly mature (grade 1 or 2)
 - Exclusively immature (grade 3 or malignant)

TOP DIFFERENTIAL DIAGNOSES

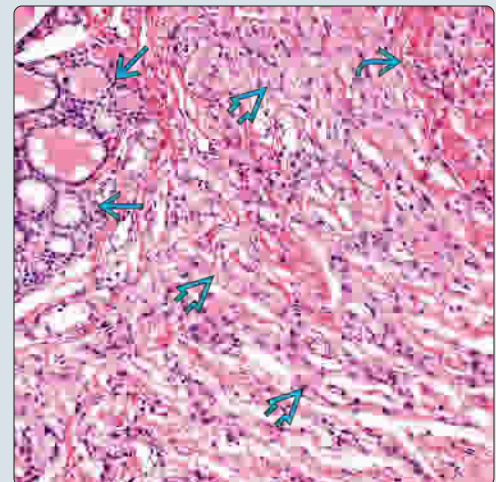
- Dermoid
- Lymphangioma
- Small blue round cell tumor (only for malignant teratoma)

Teratoma Recapitulating Fetal Trachea

(Left) This area of mature benign teratoma shows a fetal trachea. Note the cartilage [red box], minor mucoserous glands [green box], and respiratory-type epithelium [blue box] lining the lumen of the primitive structure. Thyroid follicles [yellow box] are noted adjacent to the cartilage. (Right) By definition, thyroid gland tissue must be present to qualify the tumor as a thyroid teratoma. The thyroid tissue [yellow box] is immediately adjacent to mature glial tissue [green box] juxtaposed to skeletal muscle [red box].

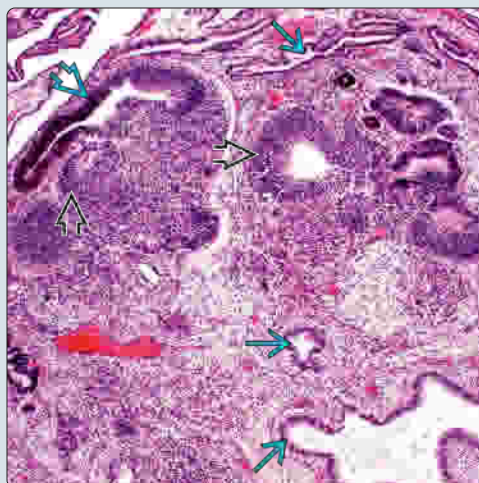


Thyroid Gland Parenchyma

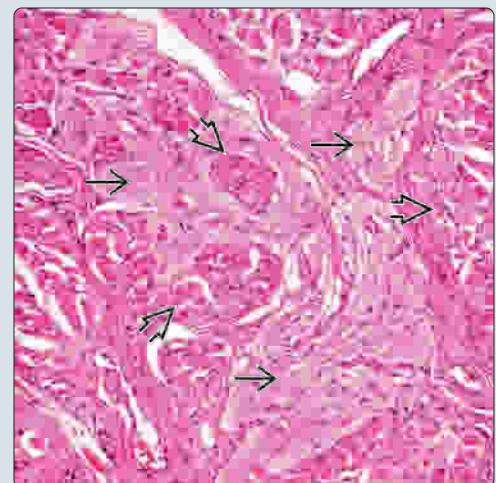


Pigmented Retinal Anlage in Teratoma

(Left) Pigmented retinal anlage [red box] is noted within more primitive or immature neuroblastomal tissue. The neural tissue contains Flexner-Wintersteiner rosettes [green box]. Note the glandular epithelium [blue box] immediately adjacent to the neural tissue (immature, benign). (Right) Each of the 2 elements in this image are benign, mature, and "normal," although not in this arrangement: Glial tissue [green box] is noted surrounding and separating bundles of skeletal muscle [red box].



Benign and Mature Elements in Teratoma



TERMINOLOGY

Synonyms

- Only **teratoma** has trilineage differentiation
- Other terms **incorrectly** used include choristoma, hamartoma, epignathus, heterotopia, dermoid

Definitions

- Tumor of germ cell derivation composed of mature or immature tissues derived from all 3 germ cell layers
 - Ectoderm, mesoderm, and endoderm
- Defined as **thyroid** teratomas if
 - Tumor occupies portion of thyroid gland or there is direct continuity or close anatomic relationship between tumor and thyroid gland
 - Cervical teratoma is accompanied by complete absence of thyroid gland
 - Either total replacement of gland by tumor or thyroid anlage that failed to develop into mature thyroid gland

ETIOLOGY/PATHOGENESIS

Embryonic Developmental Abnormality

- Believed to arise from misplaced embryonic germ cells (rests) in thyroid gland that continue to develop in new location

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare: < 0.1% of all primary thyroid gland neoplasms
- Age
 - Broad age range: Newborn to 85 years
 - Average: < 10 years
 - Bimodal age distribution
 - Neonates and infants: > 90% are benign teratomas
 - Children and adults: ~ 50% are malignant teratomas
- Sex
 - Equal gender distribution

Site

- Anterior neck, including thyroid gland, although separation is difficult, especially in large neonatal tumors

Presentation

- All patients present with neck mass, often remarkably large
- Frequently experience dyspnea, difficulty breathing, stridor
- Other congenital anomalies may be present in neonatal patients

Natural History

- Neonatal cases, if untreated, may result in patient death due to airway compromise &/or mass effect, irrespective of histologic grade

Treatment

- Options, risks, complications
 - Outcome depends on patient's age, tumor size at presentation, and presence and proportion of immaturity

- Surgery must be instituted immediately in neonatal cases to avoid morbidity or mortality
- Surgical approaches
 - Surgical excision for benign or immature teratomas is treatment of choice
 - If mass is detected in utero, consider delivering fetus by ex utero intrapartum treatment (EXIT) procedure
 - Fetus is partially delivered by cesarean section while placenta and umbilical cord remain intact
 - Uteroplacental gas exchange maintained and fetus remains hemodynamically stable while airway is established
 - Avoids "crash" attempt at achieving airway at birth
- Drugs
 - Chemotherapy may be used for malignant teratoma, although often palliative
- Radiation
 - Only used for malignant teratoma, but considered palliative in most cases

Prognosis

- Age at presentation and tumor histology are strongly correlated
 - Neonates and infants: Nearly all are benign or immature teratomas (grade 0, 1, or 2)
 - Children and adults: Preponderance of malignant teratomas (grade 3)
- No patients with grade 0, 1, or 2 tumor (benign mature or benign immature) die **from** disease, although some die **with** disease
 - Death is generally direct result of significant morbidity secondary to tracheal compression or lack of development of vital structures in neck during fetal growth
 - Surgery for neonatal thyroid teratomas must be instituted immediately to avoid preoperative morbidity (mass effect) and mortality
- Malignant teratomas exhibit clinically aggressive behavior
 - May invade by direct extension into esophagus, trachea, salivary glands, &/or soft tissues of neck
 - Recurrence and dissemination (usually in lungs) occur in ~ 1/3 of patients
 - Many of these cases are fatal

IMAGING

Radiographic Findings

- Ultrasonographic images (in utero, at time of birth, or later) provide best information and are easiest to obtain
 - Most common finding is multicystic mass of thyroid gland
- CT shows inhomogeneous mass arising in thyroid gland

MACROSCOPIC

General Features

- Tumor surface is smooth to bosselated or lobulated
- Tumor periphery is well circumscribed to widely infiltrative into surrounding thyroid parenchyma
- Consistency varies from firm to soft and cystic
- Multiloculated cystic spaces

Histologic Grading of Thyroid Teratomas

Histologic Feature	Histologic Category and Grade
Mature elements only	Benign, mature = grade 0
≤ 1 low-power field (4x objective and 10x ocular) of immature elements	Benign, immature = grade 1
> 1 but ≤ 4 low-power fields of immature foci	Benign, immature = grade 2
> 4 low-power fields of immature elements, along with mitoses and cellular atypia	Malignant = grade 3
<i>Based on proposed system: Thompson LD et al: Primary thyroid teratomas: a clinicopathologic study of 30 cases. Cancer. 88(5):1149-58, 2000.</i>	

- Spaces are filled with white-tan creamy material, mucoid glairy material, or dark brown hemorrhagic fluid admixed with necrotic debris
- Tissue resembling brain is seen, often associated with black pigmentation (retinal anlage)
- Gritty bone or cartilage is frequently noted
- Gray-tan or yellow-white to translucent cut surface

Sections to Be Submitted

- Periphery to document thyroid gland involvement

Size

- Mean: 6-7 cm; range: Up to 14 cm
- Larger tumors are associated with compression symptoms (stridor, hoarseness, difficulty breathing)

MICROSCOPIC

Histologic Features

- Tissues from all 3 primordial layers
 - Ectoderm, mesoderm, and endoderm
- By definition, thyroid parenchyma should be identified
 - May be scarce or absent in malignant teratomas
- Wide array of tissue types and growth patterns
 - Interrelationship and percentage of each element used to classify tumors into 1 of 3 types: Benign (mature), benign (immature), or malignant
- Small cystic spaces to solid nests
- Variety of different epithelia
 - Squamous epithelium (simple and stratified)
 - Pilosebaceous and other adnexal structures are seen
 - Pseudostratified ciliated columnar epithelium (respiratory)
 - Cuboidal glandular epithelium (± goblet cells)
 - Transitional epithelium
 - True organ differentiation (pancreas, liver, or lung) can be found
- Neural tissue (ectodermal derivation) is most common element
 - Mature glial tissue, choroid plexus, pigmented retinal anlage
 - Immature neuroblastomal elements
 - Immature tissues resemble embryonic tissue
 - Primitive neuroepithelial small- to medium-sized cells with high nuclear:cytoplasmic ratio
 - Arranged in sheets or rosette-like structures (Homer Wright or Flexner-Wintersteiner types)
 - Nuclear chromatin is hyperchromatic
 - Mitoses are common
- Mesenchymal tissues intermixed with other components

- Cartilage, bone, striated skeletal muscle, smooth muscle, adipose tissue, and loose myxoid to fibrous embryonic mesenchymal connective tissue
- Maturation and relative proportions of immature neuroectodermal tissue determines grade

ANCILLARY TESTS

Cytology

- Smears are cellular, but frequently misinterpreted as "missed" or "contamination"

Immunohistochemistry

- Not used for mature or benign teratomas
- Immature components highlighted with markers specific to tissue source
 - Glial components: S100 protein, GFAP, neuron specific enolase, neural filament protein
 - Skeletal muscle: Desmin, MYOD1, myogenin, myoglobin

DIFFERENTIAL DIAGNOSIS

Dermoid

- Histology limited to only skin elements

Lymphangioma

- Clinically, lateral rather than midline
- Cystically dilated vessels filled with fluid, lymphocytes, with smooth muscle walls

Small Blue Round Cell Tumor

- Only for malignant teratoma
 - Ewing sarcoma, rhabdomyosarcoma, small-cell carcinoma, lymphoma, melanoma
 - Age and histology frequently make separation, with immunohistochemistry useful in some cases

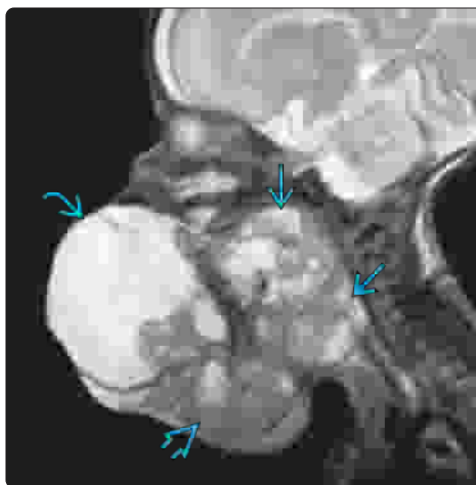
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Clinical Photo of Large Cervical Teratoma



MR of Large Benign Immature Teratoma



(Left) Clinical photograph shows a neonate who had an anterior neck mass detected by an in utero ultrasound. The airway was compromised, and a tracheostomy was placed using the ex utero intrapartum procedure (EXIT) procedure. (Right) Sagittal T2-weighted MR shows posterior extension of the mass into the airway. The mass contains both high signal cystic areas and low signal soft tissue components typical of a teratoma. The diagnosis was a benign immature teratoma.

US of Large Cervical Teratoma

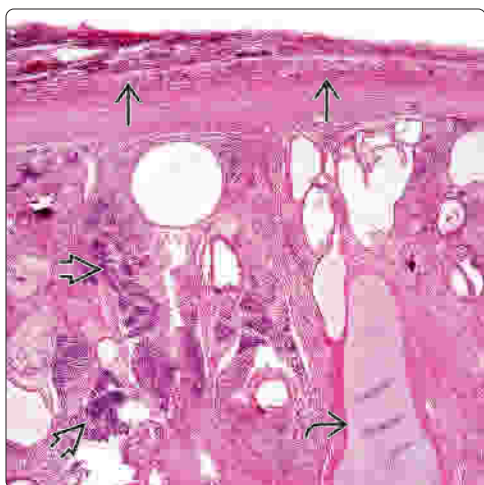


Gross Pathology From Thyroid Teratoma



(Left) This ultrasound demonstrates a large mass with the neck of this infant. There is remarkable airway displacement and compression. (Right) Gross image shows a typical example of a thyroid teratoma. The mass was approximately the same size as the fetal head from which it was removed. Note the complex cystic and solid components typical of a teratoma.

Thyroid Gland Tissue at Periphery of Teratoma



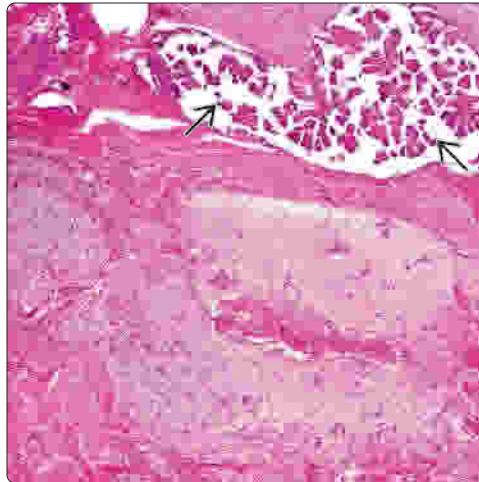
Organoid Appearance of Mature Teratoma



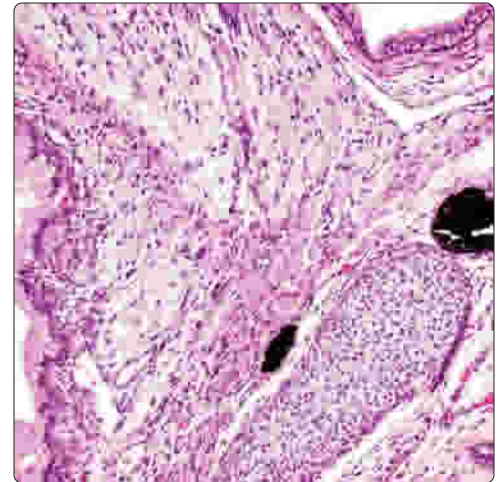
(Left) Thyroid gland parenchyma at the periphery is separated from the teratoma by a fibrous capsule. There is mature cartilage, immature glial tissue, and a number of cystic spaces lined by various epithelia. This is a benign, immature teratoma. (Right) There is a vague organoid appearance to this teratoma, showing a trachea and primitive esophagus adjacent to cystic epithelial structures, with glandular elements. Thyroid follicles are entrapped within the tumor.

Mature Glial Tissue in Teratoma

(Left) It is not uncommon for a benign, mature teratoma to have mature glial tissue immediately adjacent to the choroid plexus [B], as shown in this teratoma. The presence of neural tissue helps to separate teratomas into various grades. **(Right)** Mature elements from the primordial layers are present here, including cartilage, pigmented retinal anlage, respiratory epithelium, and mucinous epithelium separated by mature glial tissue in this benign, mature teratoma.

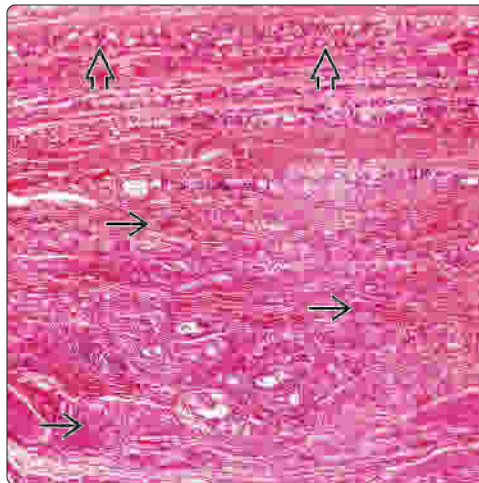


Pigmented Retinal Anlage

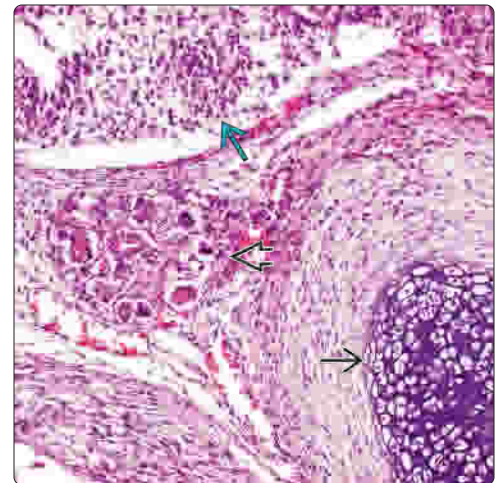


Glial Elements "Hidden" in Fibrosis

(Left) Mature glial elements [B] can sometimes be difficult to identify, as seen in this image. Note the areas of thyroid follicular epithelium [B]. Immunohistochemistry can be very helpful in highlighting the various elements in the tumor. **(Right)** This field demonstrates the remarkable juxtaposition of various elements in a teratoma, including cartilage [B], pancreas [B], and immature glial tissue [B]. This is a benign, immature teratoma.

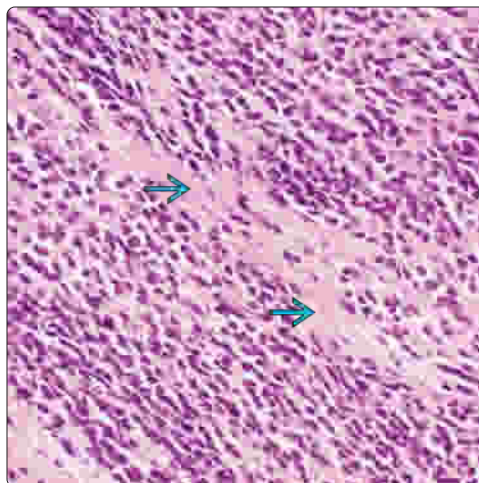


Cartilage, Pancreas, and Immature Glial Tissue

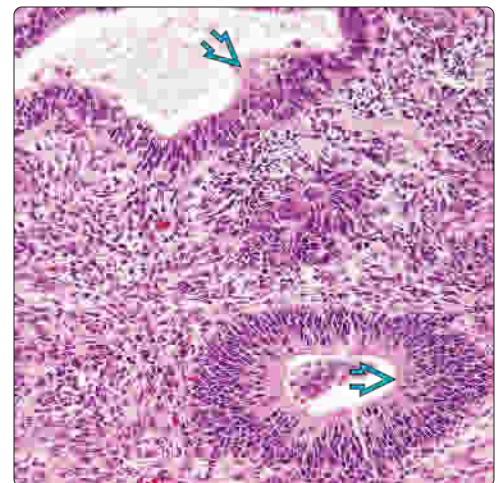


Immature Teratoma With Neuroblastoma-Like Features

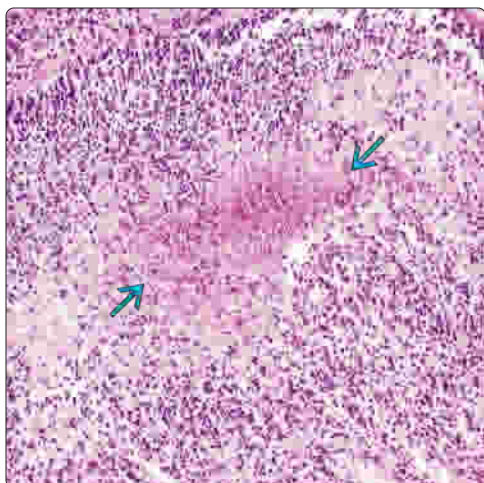
(Left) Primitive, immature neuroblastoma tissue fills this field, with a vague Homer Wright-type rosette created with the neural-fibrillar matrix material in the center [B]. If this finding is dominant, the tumor is either immature or malignant, depending on the number of foci. **(Right)** Rosettes are usually identified within the immature neural elements. In this case, there are very characteristic Flexner-Wintersteiner rosettes [B], showing a well-formed, gland-like lumen. Note the immature neural tissue in the rest of the field.



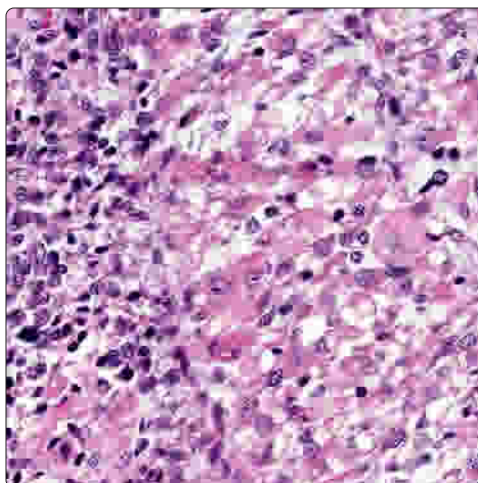
Rosettes in Immature Teratoma



Malignant Teratoma With Necrosis

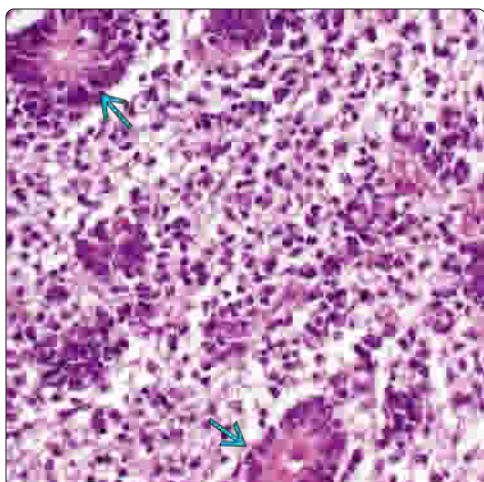


Skeletal Muscle and Immature Muscle

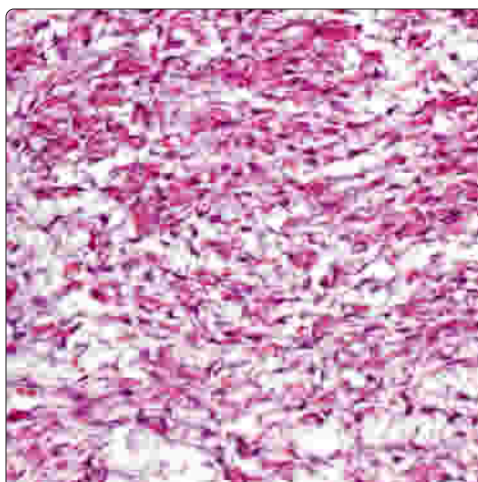


(Left) The immature blastoma is surrounding an area of tumor necrosis [B], a feature diagnostic for a malignant (grade 3) teratoma. Necrosis and increased mitoses are frequent in malignant teratoma. (Right) This immature region of a malignant teratoma shows features of rhabdoid differentiation, with a strap-cell configuration. These types of cells would be immunoreactive with myogenin or MYOD1.

Rosettes and Immature Glial Tissue

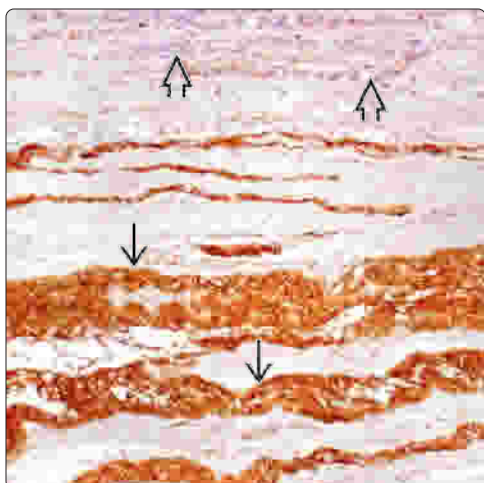


Primitive Skeletal Muscle

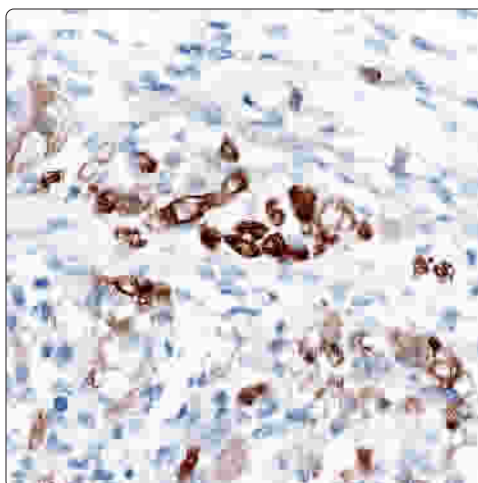


(Left) There are several rosettes [B] in this field along with areas of immature glial-type tissue. This is an example of an immature area in a teratoma. (Right) There are immature skeletal muscle fibers in this field of a thyroid gland teratoma. The tumor cell spindling with cross striations helps confirm the immature nature of the proliferation.

S100 Protein Highlights Glial Elements



Myoglobin Highlights Muscle Foci



(Left) This image shows how S100 protein highlights the mature glial elements [B]. These same areas would also be immunoreactive with GFAP. Note the areas of thyroid follicular epithelium [C], which lack S100 protein staining. (Right) When immature areas are evaluated, it may be necessary to confirm the nature of the cells with immunohistochemistry, as shown by the myoglobin immunoreactivity in this case. Keratin, myogenin, and CD99 among others can be useful.

Ectopic Hamartomatous Thymoma

KEY FACTS

TERMINOLOGY

- Benign tumor in cervical neck soft tissues exhibiting differentiation toward thymic tissue

ETIOLOGY/PATHOGENESIS

- Thought to arise from misplaced branchial pouch derivatives

CLINICAL ISSUES

- Strong male predilection (~ 20:1)
- Principally involve lower neck region, usually in close proximity to sternoclavicular joint
- May lie in proximity to thyroid gland but rarely involves thyroid gland
- Indolent behavior

MACROSCOPIC

- Solitary lobular, or multilobular mass that may be quite large ranging from 2-19 cm in greatest dimension

MICROSCOPIC

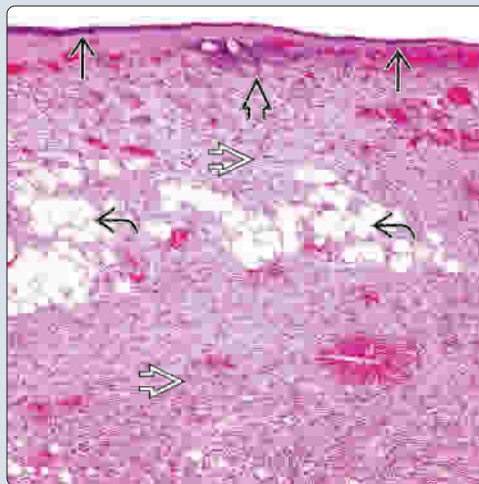
- Typically well marginated or circumscribed
- Primarily composed of epithelial cells that are spindle-shaped or mesenchymal-like with fascicular to storiform growth
 - Absence of nuclear atypia, mitotic figures, and necrosis
- Other components that may focally be present include
 - Solid squamous nests
 - Epithelial-lined cysts
 - Thin anastomosing strands of epithelial cells that may include clear cells
- Islands of mature adipose tissue and clusters of small lymphocytes may be present

ANCILLARY TESTS

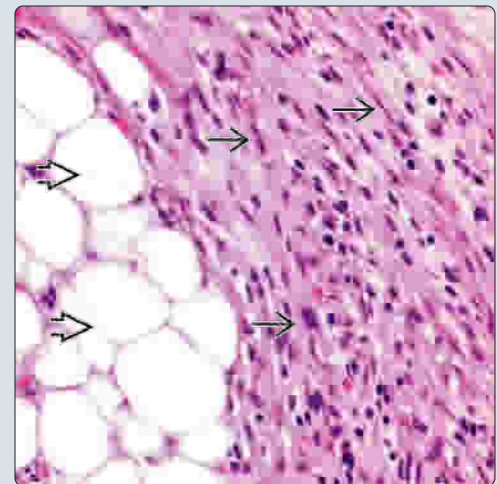
- Spindle cells: Cytokeratin (+) (strong and diffuse), muscle-specific actin, androgen receptor (nuclear) (+)
- Tonofilaments and desmosomes observed in spindle cells indicative of epithelial origin

Cervical Neck Cystic Epithelial-Lined Lesion

(Left) Cervical soft tissue cystic lesion primarily composed of spindle-shaped cells is lined by a thin layer of epithelial cells with subjacent nests of squamous cells and islands of mature adipose tissue. **(Right)** Spindle-shaped cells that lack significant nuclear pleomorphism or increased mitotic activity are admixed with mature adipose tissue and mature lymphocytes. The spindle cells are of epithelial origin as determined by their immunoreactivity and ultrastructural findings (not shown).

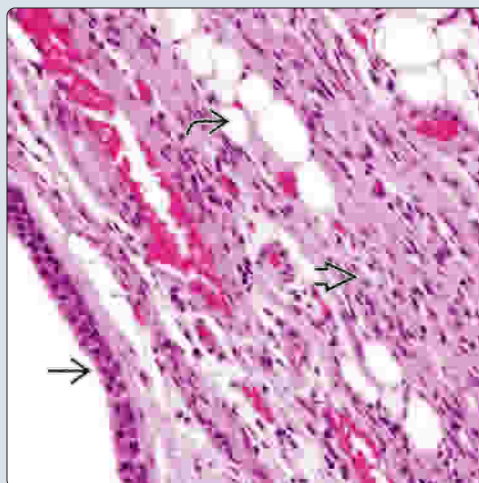


Admixture of Spindle Cells and Fat

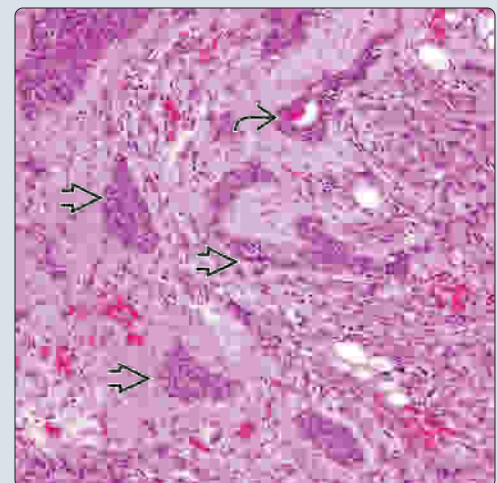


Epithelial-Lined Cyst

(Left) The cystic epithelial lining includes cuboidal cells juxtaposed to benign-appearing spindle-shaped cells that include admixed foci of mature adipose tissue in the cyst wall. **(Right)** The epithelial component also includes nests and strands of squamous epithelium focally with cystic change. The combination of cell types in a neck mass (approximating or rarely in the thyroid gland) should engender consideration for a diagnosis of ectopic hamartomatous thymoma.



Epithelial Cords and Nests



TERMINOLOGY

Definitions

- Benign tumor in cervical neck soft tissues exhibiting differentiation toward thymic tissue

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Thought to arise from misplaced branchial pouch derivatives
 - Myoepithelial branchial anlage differentiation suggested but not supported
 - No compelling evidence for thymic differentiation

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare tumor
- Age
 - Range: 3rd-8th decades (mean: 47 years; median: 40 years)
- Sex
 - Strong male predilection (~ 20:1)

Site

- Principally involve lower neck region, usually in close proximity to sternoclavicular joint
 - May lie in proximity to thyroid gland but rarely involves thyroid gland

Presentation

- Slow growing subfascial swelling in suprasternal or supraclavicular region

Treatment

- Options, risks, complications
 - Complete surgical resection is treatment of choice

Prognosis

- Indolent behavior
- Tumors may locally recur but do not metastasize or cause tumor-related death
- Rarely, adenocarcinoma may arise in ectopic hamartomatous thymoma

MACROSCOPIC

General Features

- Solitary, lobular or multilobular mass that may be quite large, ranging from 2-19 cm in greatest dimension

MICROSCOPIC

Histologic Features

- Typically well margined or circumscribed
- Primarily composed of epithelial cells that are spindle-shaped or mesenchymal-like with fascicular to storiform growth
 - Other components that may focally be present include
 - Solid squamous nests and epithelial-lined cysts
 - Thin anastomosing strands of epithelial cells that may include clear cells

- Islands of mature adipose tissue and clusters of small lymphocytes may be present
- Absence of nuclear atypia, mitotic figures, and necrosis
- Areas of skin adnexal differentiation reported (including sebaceous, eccrine, and apocrine elements)

ANCILLARY TESTS

Immunohistochemistry

- Spindle cells: Cytokeratin (+) (strong and diffuse), muscle-specific actin, androgen receptor (nuclear) (+)

Electron Microscopy

- Tonofilaments and desmosomes observed in spindle cells indicative of epithelial origin

DIFFERENTIAL DIAGNOSIS

Ectopic Cervical Thymoma

- Benign tumor that can be locally invasive and exceptionally metastasize
- Histologically identical to mediastinal thymomas
 - Residual ectopic thymus not uncommonly identified in periphery of tumor

Spindle-Cell Epithelial Tumor With Thymus-Like Differentiation

- Highly cellular tumors comprised of compact bundles of long spindle epithelial cells merging with tubulopapillary structures &/or mucinous glands

Carcinoma Showing Thymus-Like Differentiation

- Malignant neoplasm histologically similar to thymic carcinoma (lymphoepithelioma or squamous cell)

Synovial Sarcoma

- Limited (not diffuse and strong) cytokeratin reactivity
- Immunoreactivity for TLE1, Bcl-2, CD99, FLI-1, others

Malignant Peripheral Nerve Sheath Tumor

- S100 protein (+) (limited in higher grade tumors)
- Absence of cytokeratin reactivity

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Solitary Fibrous Tumor

KEY FACTS

TERMINOLOGY

- Mesenchymal tumor composed of collagen-producing spindle cells arranged in characteristic vascular pattern
 - In morphologic spectrum of solitary fibrous tumor → hemangiopericytoma

CLINICAL ISSUES

- Female > male
- Middle-aged patients; mean: 48 years
- Asymptomatic enlarging neck mass
- Excellent long-term prognosis

MACROSCOPIC

- Well circumscribed and frequently encapsulated
- Firm, solid, white-gray-tan cut appearance
- Usually large; mean: ~ 4.5 cm

MICROSCOPIC

- Infiltrative pattern, trapping thyroid follicles

- Variegated, cellular, mesenchymal proliferation
- Hypocellular areas alternate with hypercellular areas
- Patternless proliferation of bland, monotonous, spindle-shaped cells
 - Spindled with elongated, slender nuclei surrounded by scant cytoplasm
- Cells separated by bundles of ropy, keloid-like collagen
- Delicate, open vascular spaces
- Extravasated erythrocytes, inflammatory cells, and mast cells are common


ANCILLARY TESTS

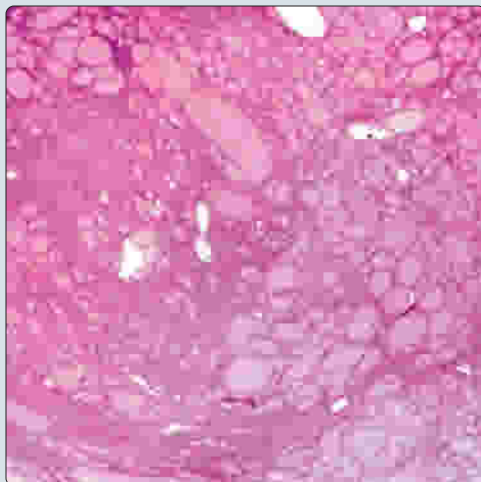
- **Positive:** STAT6, CD34, CD99, Bcl-2, vimentin

TOP DIFFERENTIAL DIAGNOSES

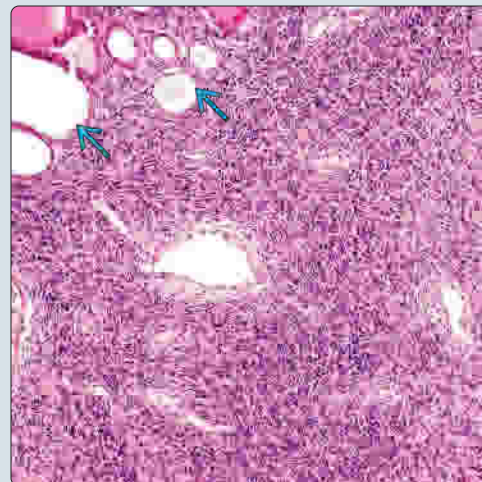
- Schwannoma, leiomyoma, spindle cell follicular adenoma, hyalinizing trabecular adenoma, post fine-needle aspiration site, medullary carcinoma

Permeation of Thyroid Follicles



(Left) Although tumors can show well-demarcated and encapsulated lesions, an infiltrative pattern can be seen, as noted in this case with permeation between the thyroid follicles. (Right) An infiltrative pattern can be seen with trapping of thyroid follicles , as shown in this case of solitary fibrous tumor (SFT). Note the cellular mesenchymal proliferation associated with patulous, open vessels.

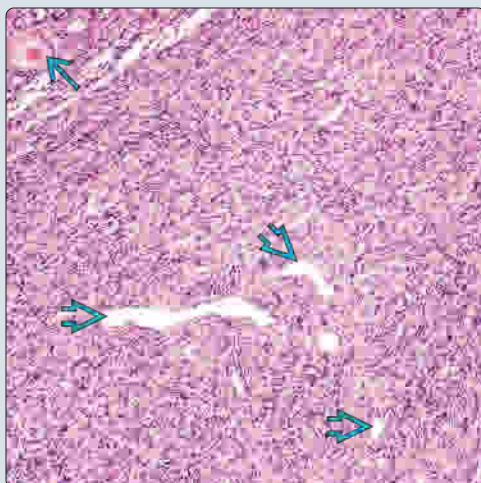


Hypercellular Proliferation

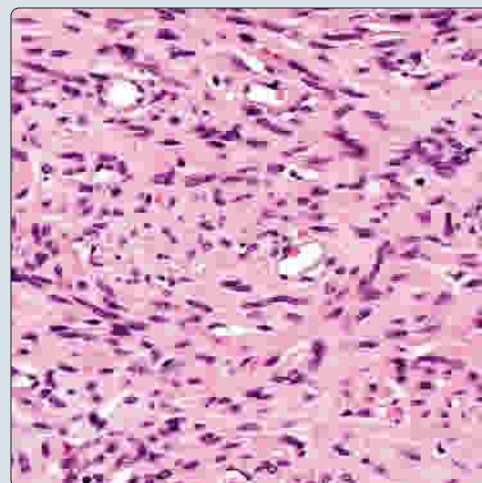


Patulous Vessels

(Left) The thyroid follicles  are uninvolved. The spindled cells are arranged in a nonspecific, syncytial architecture, with a background of delicate, open to patulous vascular spaces . (Right) There are bland, monotonous, spindle-shaped cells without any specific growth pattern, although there is a vague fascicular appearance in this case. The cells have a syncytial appearance.



Monotonous Spindled Cells



TERMINOLOGY**Abbreviations**

- Solitary fibrous tumor (SFT)

Definitions

- Mesenchymal tumor composed of collagen-producing spindle cells arranged in characteristic vascular pattern

ETIOLOGY/PATHOGENESIS**Pathogenesis**

- Primitive mesenchymal cell capable of myofibroblastic &/or fibroblastic differentiation

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Exceedingly rare thyroid neoplasm
- Age
 - Middle-aged patients; mean: 48 years
- Sex
 - Female > male

Presentation

- Asymptomatic slowly enlarging neck mass (over years)
- Hoarseness may be present

Treatment

- Lobectomy is sufficient therapy

Prognosis

- Excellent prognosis without recurrence/metastasis

MACROSCOPIC**General Features**

- Well circumscribed and frequently encapsulated
- Firm, solid, white-gray-tan cut appearance
- Cystic change occasionally, but no necrosis or calcification

Size

- Usually large; mean: ~ 4.5 cm

MICROSCOPIC**Histologic Features**

- Arise within thyroid gland or immediately adjacent soft tissues
- Develops along morphologic spectrum from benign to malignant
- Well-defined border or capsule, but may be infiltrative with trapping of thyroid follicles
- Variegated, cellular, mesenchymal proliferation
- Hypocellular and hypercellular areas alternate
- Bland, monotonous, spindle-shaped cells without any specific growth pattern
 - Storiform, fascicular, or herringbone patterns
 - Cells are spindled with elongated, slender nuclei surrounded by scant cytoplasm
 - Cells give syncytial appearance
 - Nuclear chromatin is delicate, fine to vesicular
- Cells separated by bundles of ropy, keloid-like collagen

- Background has delicate, open to patulous vascular spaces
 - Vessels not dominant, but may have thick walls
- Extravasated erythrocytes, inflammatory cells, and mast cells are common
- Uncommon: Cysts, myxoid change, lipomatous features
- Mitoses are rare and necrosis is absent

ANCILLARY TESTS**Cytology**

- Smears tend to be paucicellular
- Dyscohesive, slender, spindle-shaped cell population
- Interspersed by fragments of collagenized stroma

Immunohistochemistry

- **Positive:** STAT6, CD34, CD99, Bcl-2, vimentin
 - S100 protein may highlight fat cells
 - Focal actin reactivity reported
- **Negative:** TTF-1, thyroglobulin, FVIIIIRAg, calcitonin, HMB-45, EMA, ALK1, desmin, CD117, keratins

DIFFERENTIAL DIAGNOSIS**Peripheral Nerve Sheath Tumors**

- Antoni A and B areas, wavy nuclei, tapered cells, perivascular hyalinization
- **Positive:** S100 protein, SOX10, focal CD34

Smooth Muscle Tumors

- Short to sweeping fascicular arrangement with oval nuclei with blunt ends
- Tends to lack collagen deposition
- **Positive:** Actins, desmin; **negative:** STAT6, CD34, Bcl-2

Spindle Cell Follicular Adenoma

- Lacks collagen while showing colloid production
- **Positive:** Pancytokeratin, TTF-1, thyroglobulin

Hyalinizing Trabecular Adenoma

- Hyalinization is intra- and intercellular
- Trabecular arrangement of follicular epithelial cells
 - Perpendicular nuclei, inclusions, and yellow bodies
- **Positive:** TTF-1, thyroglobulin, Ki-67 (membranous)

Post Fine-Needle Aspiration Site



- Localized phenomenon adjacent to nodule with hemosiderin, extravasated erythrocytes, reactive vascular pattern

Medullary Carcinoma

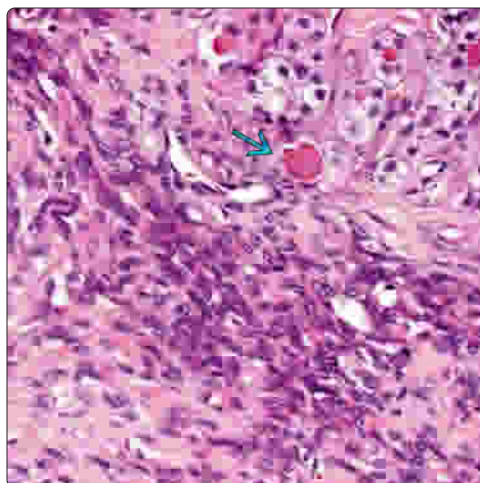
- Tumor cells can be spindled, but **positive:** Calcitonin, CEA, chromogranin, TTF-1, cytokeratin

SELECTED REFERENCES

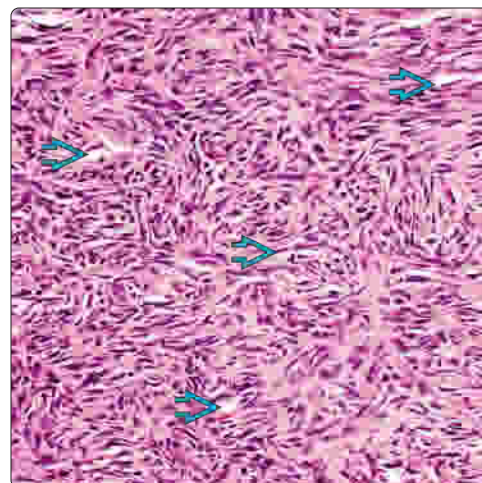
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(Left) There is a streaming arrangement to the spindled cells in this SFT of the thyroid gland. The thyroid follicles  are easily identified. **(Right)** This tumor is arranged in a storiform pattern. It is hypercellular with slit-like vessels, which are quite difficult to identify . The neoplastic cells are spindled and monotonous.

Clusters of Spindled Cells

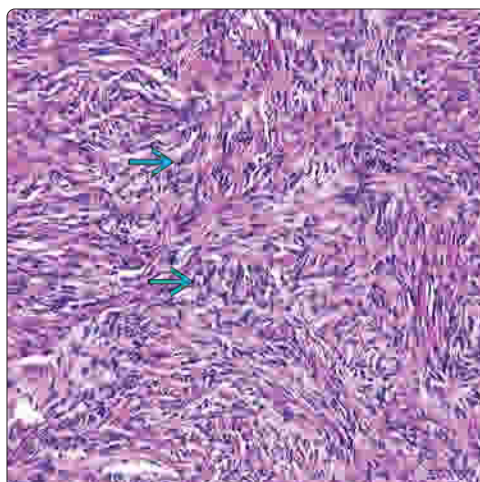


Short Fascicles to Storiform Pattern

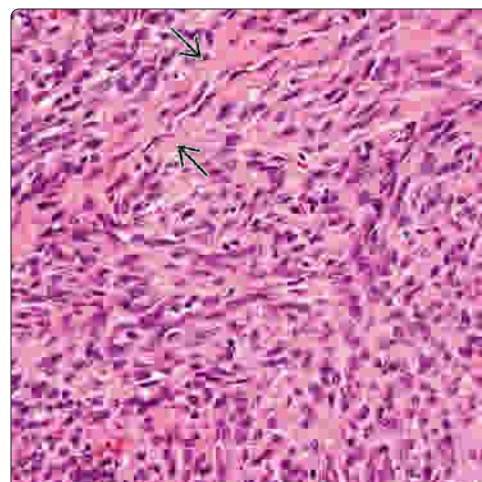


(Left) There is a haphazard and storiform appearance to this tumor. Note the suggestion of nuclear palisading  in this tumor that has a syncytial arrangement of cells. There is collagen deposition, although it is not prominent. **(Right)** The neoplastic cells are spindled with elongated, slender nuclei surrounded by scant cytoplasm. There is a syncytial appearance to the proliferation. There is collagen deposition  around a vessel.

Nuclear Palisading With Syncytial Cells

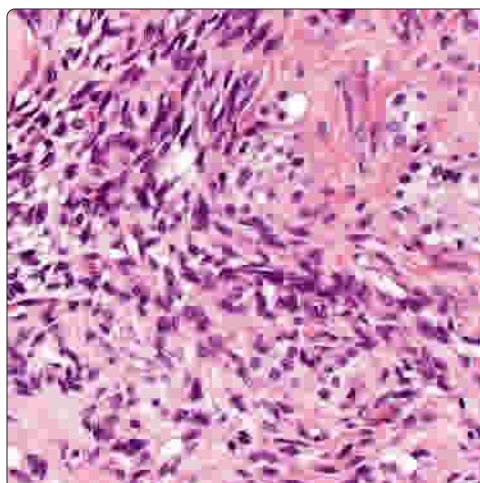


Elongated Patulous Vessels

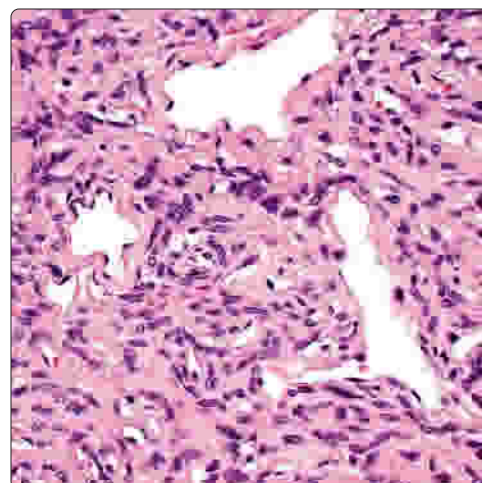


(Left) The spindled neoplastic cells are separated by bundles of keloid-like collagen in this case. Note the areas of clear cell change. This is not a lipomatous variant. **(Right)** The vascular pattern can sometimes be more prominent, suggesting the relationship to hemangiopericytoma. The cells are noted surrounding these vessels. Mitoses are usually inconspicuous.

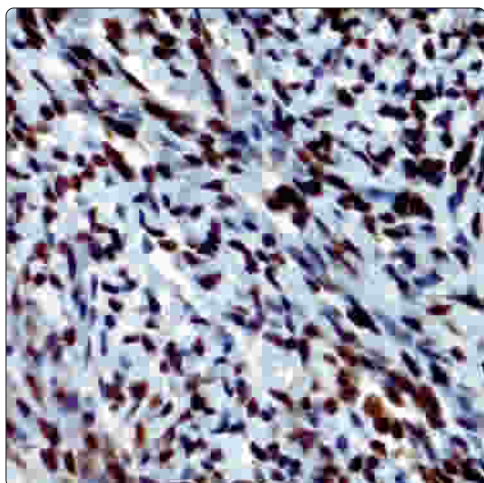
Ropy to Keloid-Like Collagen



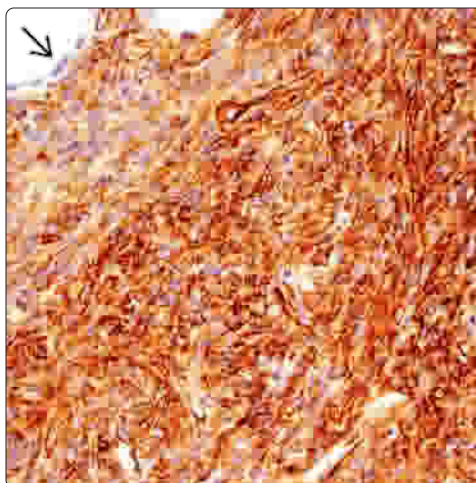
Staghorn Patulous Vessels




Strong Nuclear STAT6 Reactivity

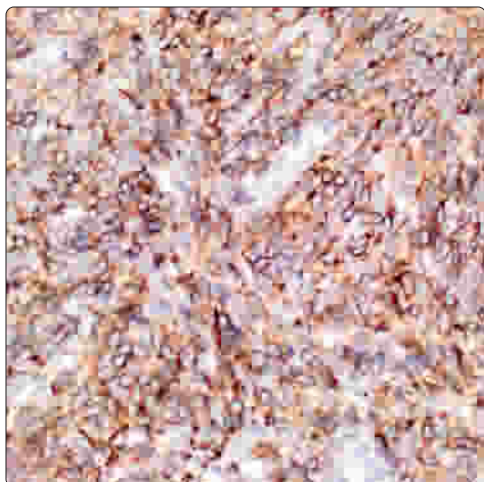


Strong, Diffuse CD34 Reaction

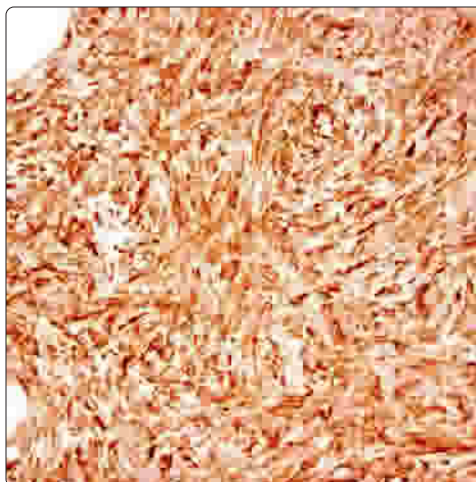


(Left) SFT shows a strong and diffuse nuclear reaction with STAT6, a helpful marker in the differential diagnostic considerations. (Right) While usually not required for the diagnosis, there is usually strong and diffuse immunoreactivity with vimentin, CD34, and Bcl-2. The CD34 is 1 of the most commonly immunoreactive. Note the thyroid follicle is negative .

Bcl-2 Highlights Neoplastic Cells

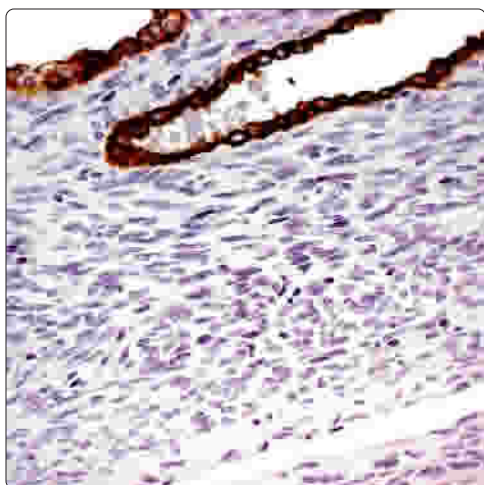


Strong, Diffuse Bcl-2 Reaction

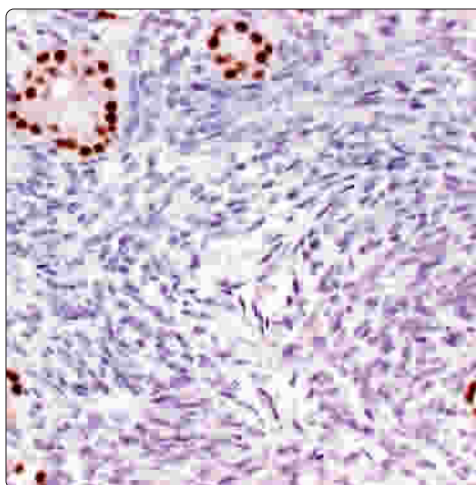


(Left) The neoplastic cells of SFT are shown here to be reactive with Bcl-2, one of several markers that can be seen in this tumor. (Right) In this case, there is strong and diffuse Bcl-2 immunoreactivity, quite similar to CD34. If STAT6 is not available, a combination of these 2 stains will help to confirm the diagnosis.

Negative Thyroglobulin Stain



TTF-1 Highlights Entrapped Follicular Cells



(Left) If there is a question about the diagnosis, and the possibility of an undifferentiated or other spindled cell tumor is considered, then a negative thyroglobulin can help to support the interpretation of a mesenchymal lesion. (Right) The entrapped thyroid follicles show strong and diffuse nuclear immunoreactivity with TTF-1, highlighting the thyroid epithelium within the background of spindled cell population. This can be used to separate spindle cell follicular adenoma from SFT.

KEY FACTS

TERMINOLOGY

- Thyroid gland primary paragangliomas are intrathyroidal neuroendocrine tumors of paraganglionic origin
 - Probably arise from inferior laryngeal paraganglia (neural crest)

CLINICAL ISSUES

- Wide range (9-78 years); mean: 48.2 years
- Female > male (5.3:1)
- Asymptomatic neck mass, without active hormone secretion
- Surgical excision is treatment of choice
- Nearly all thyroid gland paragangliomas are benign

MACROSCOPIC

- Circumscribed, intrathyroidal mass; mean: 3 cm

MICROSCOPIC

- Well-circumscribed, encapsulated intrathyroidal mass

- Highly vascular, with rich vascular plexus
- Tumor cells arranged in alveolar, lobular, sheet, or zellballen pattern
- Paraganglia chief cells are polygonal with abundant, granular, amphophilic cytoplasm
- Isolated pleomorphic nuclei (~ 10% of cases)
- Very rare mitoses and exceedingly rare necrosis

ANCILLARY TESTS

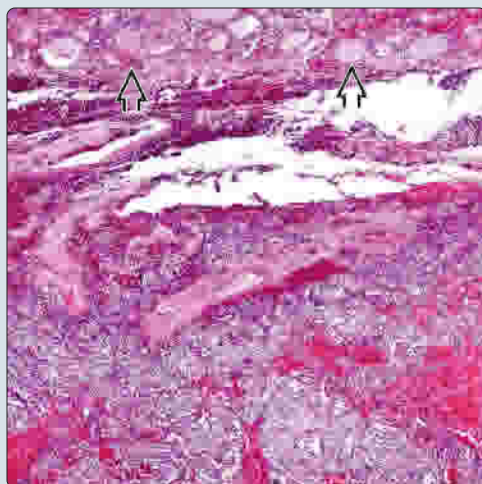
- Chief cells **positive**: Synaptophysin, chromogranin A, CD56, SDHB
- Sustentacular cells **positive**: S100 protein, GFAP
- Negative**: Cytokeratins, thyroglobulin, TTF-1, calcitonin, parathyroid hormone (PTH)

TOP DIFFERENTIAL DIAGNOSES

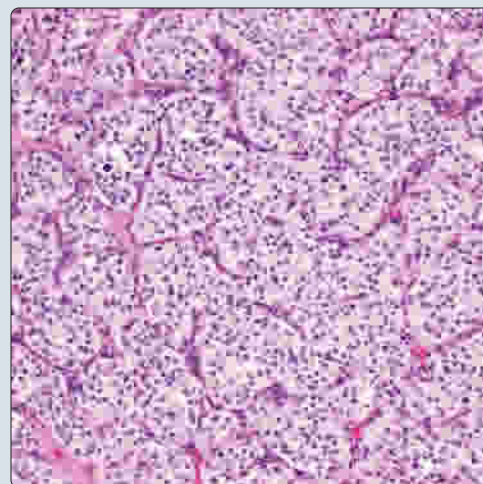
- Medullary thyroid carcinoma, hyalinizing trabecular tumor, parathyroid adenoma, metastatic neuroendocrine tumors

Partially Encapsulated Paraganglioma

(Left) There is a partially encapsulated paraganglioma in the thyroid gland. Note the uninvolved thyroid parenchyma [box]. The tumor is quite vascular with extravasated erythrocytes. (Right) The tumors are often quite cellular. There is a nested to zellballen architecture in this tumor. The neoplastic cells are of intermediate size with small, hyperchromatic nuclei.

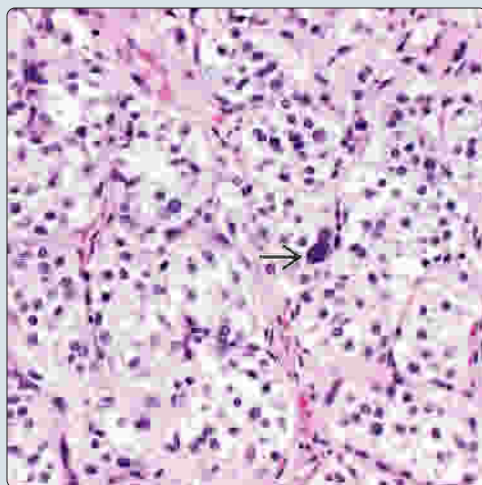


Characteristic Zellballen Architecture

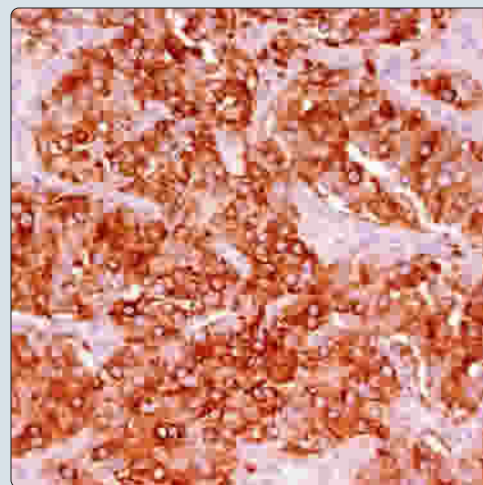


Focal Nuclear Pleomorphism

(Left) The characteristic zellballen arrangement is highlighted by delicate fibrovascular septations. The chief cells have lightly basophilic cytoplasm surrounding small nuclei. Nuclear pleomorphism is isolated [box]. (Right) The paraganglia cells are highlighted by a variety of neuroendocrine markers. In this case, chromogranin A was strongly and diffusely immunoreactive in a granular distribution.



Chromogranin A Positive Paraganglia Cells



TERMINOLOGY

Definitions

- Thyroid gland primary paragangliomas are intrathyroidal neuroendocrine tumors of paraganglionic origin
 - Functionally separated into 2 types: Sympathetic and parasympathetic
 - Most parasympathetic tumors occur in head and neck region

ETIOLOGY/PATHOGENESIS

Inherited

- While familial tumors are possible, thyroid primaries appear to be sporadic

Pathogenesis

- Probably arise from inferior laryngeal paraganglia (neural crest)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Exceedingly rare (< 0.1% of thyroid neoplasms)
- Age
 - Wide range (9-78 years); mean: 48.2 years
- Sex
 - Female > > male (5.3:1)

Presentation

- Asymptomatic neck mass, without active hormone secretion
- If multifocal tumors are found, syndrome/familial association must be considered

Treatment

- Surgical excision is treatment of choice
- Rule out multifocal disease

Prognosis

- Nearly all thyroid gland paragangliomas are benign
- Long-term clinical follow-up recommended, especially in multifocal disease

IMAGING

Radiographic Findings

- Octreotide, sestamibi, or I-131 metaiodobenzylguanidine (MIBG) scintigraphy may show tumor

MACROSCOPIC

General Features

- Circumscribed, gray-brown, intrathyroidal mass

Size

- Mean: 3 cm

MICROSCOPIC

Histologic Features

- Well-circumscribed, encapsulated intrathyroidal mass

- Extrathyroidal extension reported: Trachea, larynx, esophagus, nerves
- Highly vascular, with rich vascular plexus
 - Fibrovascular septa are delicate and discontinuous
- Tumor cells arranged in alveolar, lobular, sheet, or zellballen pattern
- Paraganglia chief cells are polygonal with abundant, granular, amphophilic cytoplasm
- Nuclei are usually round to oval, with coarse chromatin
 - Isolated pleomorphic nuclei (~ 10% of cases)
- Sustentacular supporting cells only seen with immunohistochemistry
- Very rare mitoses and exceedingly rare necrosis
- Malignancy defined by metastatic disease (although not reported in thyroid gland)

ANCILLARY TESTS

Immunohistochemistry

- Chief cells **positive**: Synaptophysin, chromogranin A, NSE, CD56, tyrosine hydroxylase, SDHB
- Sustentacular cells **positive**: S100 protein, GFAP
- Negative**: Cytokeratins, EMA, thyroglobulin, TTF-1, calcitonin, CEA-m, serotonin, parathyroid hormone

Genetic Testing

- Germline mutations in several genes encoding various subunits of succinate-ubiquinone oxidoreductase gene

DIFFERENTIAL DIAGNOSIS

Medullary Thyroid Carcinoma

- Invasive with fibrosis, amyloid and calcifications
- Positive**: Calcitonin, cytokeratin, CEA-m, synaptophysin, chromogranin A, CD56

Hyalinizing Trabecular Tumor

- Intratymoral (intratracheal) fibrosis, trabecular pattern
- Perinucleolar halos, intranuclear cytoplasmic inclusions, yellow bodies
- Positive**: TTF-1, thyroglobulin, MIB-1 (membranous)

Parathyroid Adenoma

- May have nested architecture, but cleared cells with prominent cell borders
- Positive**: PTH, chromogranin A, synaptophysin; **negative**: S100

Metastatic Neuroendocrine Tumors

- Multifocal tumor with pleomorphism (carcinoid, small cell carcinoma, Merkel)
- Spindled cells with salt and pepper chromatin
- Positive**: TTF-1, CK20, cytokeratin, synaptophysin, CD56

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- Phitayakorn R et al: Thyroid-associated paragangliomas. *Thyroid.* 21(7):725-33, 2011
- Baloch ZW et al: Neuroendocrine tumors of the thyroid gland. *Am J Clin Pathol.* 115 Suppl:S56-67, 2001
- Buss DH et al: Paraganglioma of the thyroid gland. *Am J Surg Pathol.* 4(6):589-93, 1980

KEY FACTS

TERMINOLOGY

- Benign primary thyroid neoplasm composed of cells with distinct smooth muscle differentiation histologically

ETIOLOGY/PATHOGENESIS

- May develop from smooth muscle-walled vessels at thyroid gland periphery

CLINICAL ISSUES

- Exceedingly rare (< 0.02% of all thyroid gland tumors)
- Younger patients with equal gender distribution
- Thyroid mass, usually slowly developing over years
- Lobectomy or thyroidectomy is curative
- Excellent prognosis without any reported cases of death from disease

IMAGING

- Thyroid scans with radioactive isotopes demonstrate cold nodule
- Inhomogeneous low-density mass in thyroid gland

MACROSCOPIC

- Well circumscribed, with smooth outer tumor surface
- Mean: 2 cm

MICROSCOPIC

- Encapsulated, with smooth, noninvasive periphery
- Arranged in bundles or fascicles of smooth muscle fibers that intersect in orderly fashion
- Cells are spindled and blunt-ended or cigar-shaped
- Centrally placed nuclei are slightly hyperchromatic
- Perinuclear cytoplasmic vacuoles are sometimes prominent
- No pleomorphism, necrosis, or increased mitotic figures

ANCILLARY TESTS

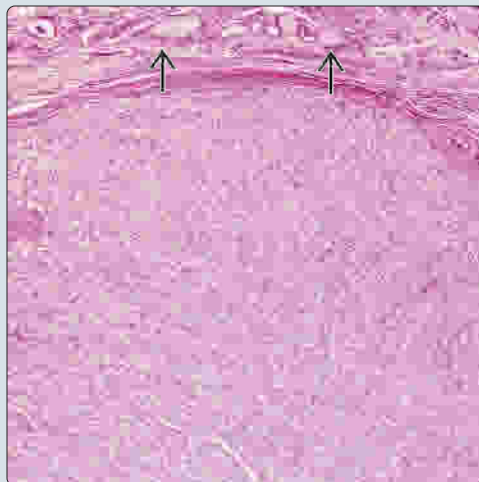
- Tumor cells **positive**: SMA, MSA, desmin, vimentin

TOP DIFFERENTIAL DIAGNOSES

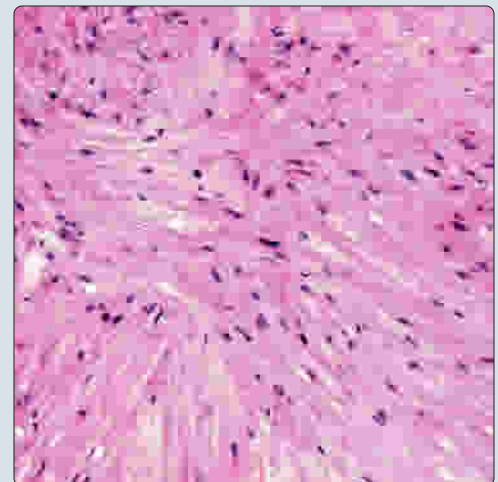
- Peripheral nerve sheath tumor, follicular spindle cell adenoma, leiomyosarcoma

Well-Circumscribed Thyroid Leiomyoma

(Left) The thyroid gland parenchyma is separated from the neoplasm by a thin, but well-formed, fibrous connective tissue capsule. The spindled cell tumor shows short, interlacing fascicles. **(Right)** On high power, there are interlacing bundles or fascicles of smooth muscle fibers that intersect in an orderly fashion. The spindled cells have blunt, centrally placed, hyperchromatic nuclei. Small vacuoles are noted in the cytoplasm of a few cells. There are no mitotic figures.

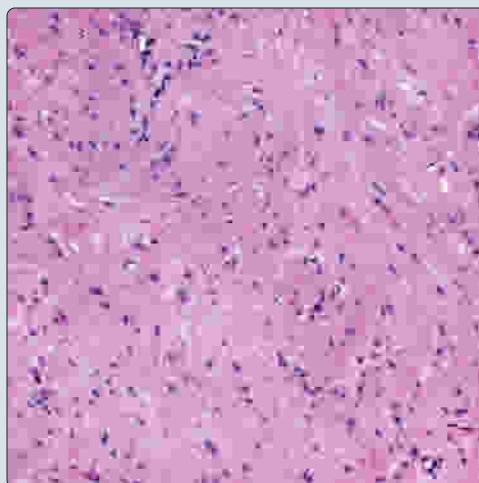


Interlacing Bundles of Smooth Muscle

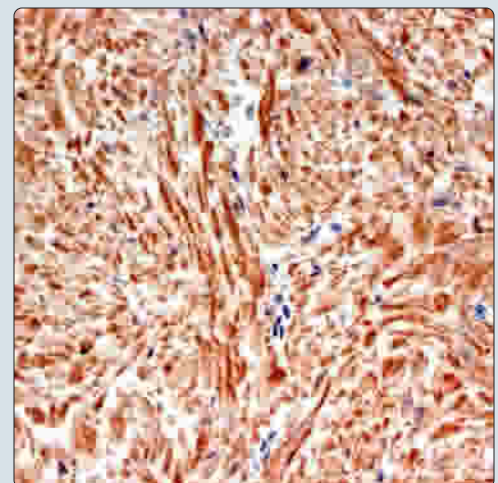


Bland Smooth Muscle Cells

(Left) The smooth muscle cells of thyroid leiomyoma are bland, with abundant spindled cytoplasm surrounding oval to spindled nuclei. There is no pleomorphism, necrosis, or increased mitoses. **(Right)** The neoplastic cells of leiomyoma are strongly and diffusely immunoreactive with a variety of muscle markers, which, in this case, is smooth muscle actin.



Strong and Diffuse Smooth Muscle Actin



TERMINOLOGY

Definitions

- Benign primary thyroid neoplasm composed of cells with distinct smooth muscle differentiation histologically

ETIOLOGY/PATHOGENESIS

Etiology

- No radiation exposure history

Pathogenesis

- May develop from smooth muscle-walled vessels at thyroid gland periphery
 - Smooth muscle tumors are classified into cutaneous and subcutaneous, deep soft tissue, and vascular origins

CLINICAL ISSUES

Epidemiology

- Incidence
 - Exceedingly rare, representing < 0.02% of all thyroid gland tumors
- Age
 - Younger patients
- Sex
 - Equal gender distribution

Site

- No specific site, although periphery of gland is more likely

Presentation

- Nonspecific signs and symptoms
- Thyroid mass, usually slowly developing
- Symptoms tend to be present for years

Laboratory Tests

- Normal thyroid function tests

Treatment

- Lobectomy or thyroidectomy is curative

Prognosis

- Excellent, without any reported cases of death from disease

IMAGING

Radiographic Findings

- Thyroid scans with radioactive isotopes demonstrate cold nodule
- Inhomogeneous low-density mass in thyroid gland
 - Signal intensity similar to surrounding soft tissue

MACROSCOPIC

General Features

- Smooth outer tumor surface
- Well circumscribed

Size

- Mean: 2 cm

MICROSCOPIC

Histologic Features

- Encapsulated, with smooth, noninvasive periphery
- Arranged in bundles or fascicles of smooth muscle fibers that intersect in orderly fashion
- Cells are spindled and blunt-ended or cigar-shaped
- Centrally placed nuclei are slightly hyperchromatic
- Perinuclear cytoplasmic vacuoles are sometimes prominent
- No pleomorphism, necrosis, or increased mitotic figures

ANCILLARY TESTS

Histochemistry

- Trichrome: Red staining of smooth muscle; blue staining of collagen

Immunohistochemistry

- **Positive:** SMA, MSA, desmin, vimentin
- Low to absent Ki-67 labeling index
- **Negative:** Thyroglobulin, TTF-1, pax-8, pancytokeratin, S100 protein, chromogranin, calcitonin

Electron Microscopy

- Spindle cells with thin myofilaments (microfilament bundles) with dense patches (dense bodies), along with discontinuous basal lamina

DIFFERENTIAL DIAGNOSIS

Peripheral Nerve Sheath Tumor

- Tumor has cellular (Antoni A) and hypocellular (Antoni B) areas
- Nuclei are wavy without perinuclear clearing
- Perivascular hyalinization is usually prominent
- Strong reactivity with S100, while negative with muscle markers

Follicular Spindle Cell Adenoma

- Circumscribed and encapsulated neoplasm
- Epithelial appearance, with colloid often identified
- Neoplastic cells **positive:** TTF-1, thyroglobulin, keratin

Leiomyosarcoma

- Infiltrative, destructive border, pleomorphism, necrosis, increased mitoses, including atypical forms

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1. Mohammed AZ et al: Leiomyoma of the thyroid gland with psammoma bodies. *Niger Med J*. 56(1):71-3, 2015
2. Papi G et al: Primary spindle cell lesions of the thyroid gland; an overview. *Am J Clin Pathol*. 125 Suppl:S95-123, 2006
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6. Andron A et al: Leiomyoma and neurilemoma: report of two unusual non-epithelial tumours of the thyroid gland. *Virchows Arch A Pathol Anat Histopathol*. 413(4):367-72, 1988
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Schwannoma

KEY FACTS

TERMINOLOGY

- Benign neoplasm composed of cells with evidence of distinct peripheral nerve sheath differentiation
- Peripheral nerve sheath tumors (PNSTs) include schwannoma and neurofibroma

ETIOLOGY/PATHOGENESIS

- May arise from sympathetic and parasympathetic or possibly sensory nerves

CLINICAL ISSUES

- Very rare (< 0.02% of all thyroid gland tumors)
- All ages affected, with equal gender distribution
- May arise from medium to large nerves at thyroid gland periphery
- Present with a thyroid gland mass
- Surgery is curative

MACROSCOPIC

- Smooth surface, well circumscribed or encapsulated

- Tan to white and glistening with neural appearance

MICROSCOPIC

- Densely packed spindle cell areas (Antoni A)
- Loosely arranged hypocellular degenerated myxoid areas (Antoni B)
- Slender spindle cells arranged in interlacing fascicles
 - Fibrillar cytoplasmic extensions
 - Palisading of nuclei (Verocay bodies)
 - Nuclei are wavy and spindled, lacking atypia
- Small to medium-sized blood vessels may have hyalinized walls



ANCILLARY TESTS

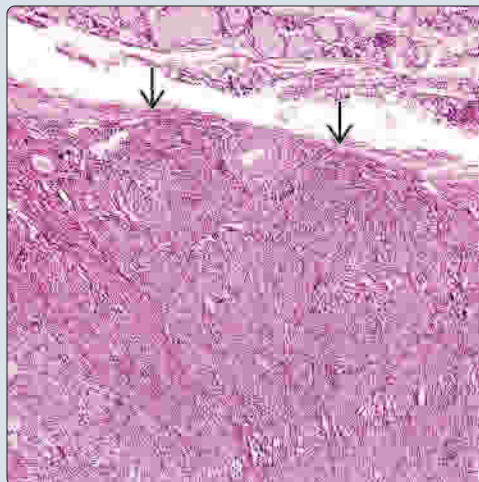
- **Positive:** S100 protein, SOX10
- **Negative:** TTF-1, calcitonin, actin, desmin

TOP DIFFERENTIAL DIAGNOSES

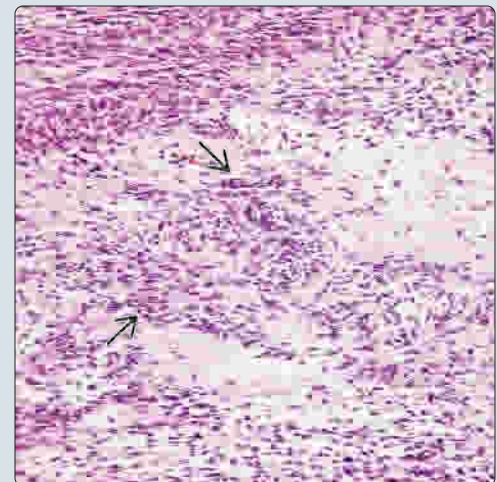
- Leiomyoma, soft tissue primary, malignant peripheral nerve sheath tumor, solitary fibrous tumor

Smooth Border to a Schwannoma


(Left) H&E shows a very well-demarcated neoplasm  adjacent to the uninvolved thyroid gland parenchyma. There is an interlacing fascicular arrangement to this neoplasm at low power, showing some areas of fibrosis. (Right) H&E shows an alternating cellular and hypocellular area to this tumor in which there is a palisading of the nuclei , a feature seen in schwannoma. The neural matrix material is easily identified. There is no pleomorphism, necrosis, or increased mitoses.

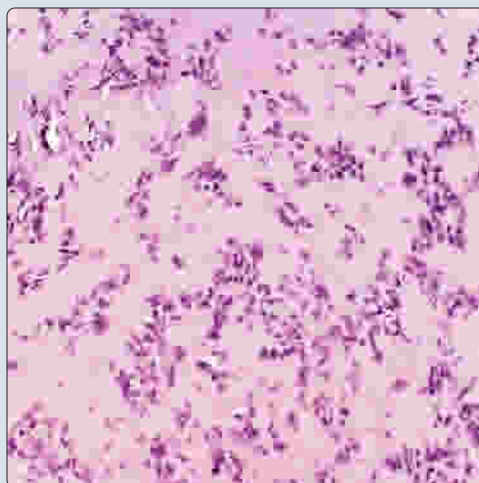


Palisaded Nuclei in Schwannoma

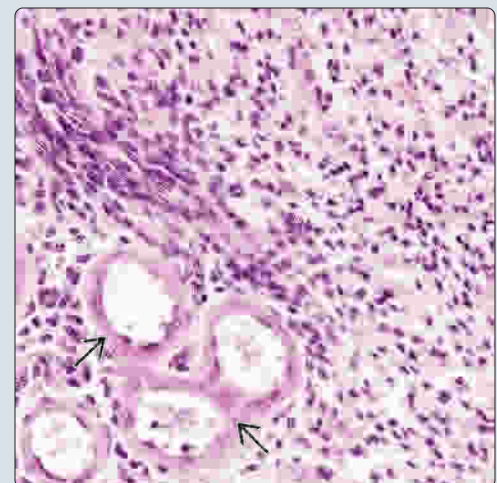


Palisaded Nuclei in Schwannoma

(Left) The nuclei show a remarkable aggregation or palisading in this schwannoma. The neural matrix material is quite hyalinized in this example of a peripheral nerve sheath tumor. (Right) There is a palisade of spindled to wavy nuclei in this area. Note that the vessels show prominent hyalinization , a feature that is quite commonly identified in schwannoma. The neural matrix is easily identified in the background of this tumor.



Perivascular Hyalinization in Schwannoma



TERMINOLOGY**Abbreviations**

- Peripheral nerve sheath tumors (PNSTs)
- Malignant peripheral nerve sheath tumors (MPNSTs)

Definitions

- Benign neoplasm composed of cells with evidence of distinct peripheral nerve sheath differentiation histologically
 - Must arise within thyroid parenchyma or be contained within capsule of thyroid gland
 - PNSTs include schwannoma and neurofibroma

ETIOLOGY/PATHOGENESIS**Pathogenesis**

- May arise from sympathetic and parasympathetic or possibly sensory nerves

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Very rare, < 0.02% of all thyroid gland tumors
 - Prevalence of PNSTs is higher among kindred with von Recklinghausen disease and neurofibromatosis
 - Although not detected in thyroid gland disease
- Age
 - All ages, although syndrome-associated tumors seen in younger patients

Site

- Medium to large nerves at periphery of gland

Presentation

- Nonspecific, although often a mass, increasing in size

Treatment

- Lobectomy or thyroidectomy is curative

Prognosis

- Excellent prognosis without death from disease

IMAGING**Radiographic Findings**

- CT images show inhomogeneous, low-density mass

MACROSCOPIC**General Features**

- Well-circumscribed or encapsulated smooth outer surface
- Tan to white and glistening with neural appearance
- Cut surface may focally appear cystic with yellow fluid

Size

- Variable, but usually smaller than MPNSTs

MICROSCOPIC**Histologic Features**

- Variably cellular but without pleomorphism or necrosis
- Densely packed spindle-cell areas (Antoni A)

- Loosely arranged hypocellular degenerated myxoid areas (Antoni B)
- Slender spindle cells arranged in interlacing fascicles
 - Fibrillar cytoplasmic extensions arranged in loose background
- Palisading of nuclei (Verocay bodies) can be seen
- Nuclei are wavy and spindled, without significant pleomorphism
 - Coarse nuclear chromatin distribution and inconspicuous nucleoli
- Rare mitoses without atypical forms
- Small to medium-sized blood vessels may have hyalinized walls
- Mast cells may be present in stroma

ANCILLARY TESTS**Cytology**

- Soft tissue neck lesions can present as thyroid primaries: Know anatomic site
- Cellular, spindled tumor cells with elongated, slender, and wavy nuclei
- Fibrillary metachromatic stroma (on air-dried Romanowsky-stained slides) may be present

Immunohistochemistry

- **Positive:** S100 protein, SOX10, vimentin
- **Negative:** Thyroglobulin, TTF-1, calcitonin, actin, desmin

Electron Microscopy

- Narrow to broad, entangled cell processes covered by discrete basement membrane substance
- Fibrous long-spacing collagen, with its distinct periodicity
- Collagen fibers are banded together and inserted into basal lamina

DIFFERENTIAL DIAGNOSIS**Leiomyoma**

- Circumscribed tumor with spindled cells, evenly cellular, with cigar-shaped nuclei and perinuclear vacuolization
- **Positive:** Actins, desmin

Soft Tissue Primary

- Exclude soft tissue tumor pushing into or abutting thyroid gland

Malignant Peripheral Nerve Sheath Tumor

- Invasive, pleomorphism, tumor necrosis, increased mitoses and higher cellularity

Solitary Fibrous Tumor

- Spindled tumor cells between ropy, keloid-like collagen deposition
- **Positive:** STAT6, CD34, bcl-2
- **Negative:** S100 protein, SOX10

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2. Papi G et al: Primary spindle cell lesions of the thyroid gland; an overview. *Am J Clin Pathol.* 125 Suppl:S95-123, 2006
3. Thompson LD et al: Peripheral nerve sheath tumors of the thyroid gland: a series of four cases and a review of the literature. *Endocr Pathol.* 7(4):309-318, 1996

KEY FACTS

TERMINOLOGY

- Increased number of Langerhans cells: Unique histiocyte-containing Birbeck granules
 - Eosinophilic granuloma:** Predominantly osseous or pulmonary isolated disease
 - Hand-Schüller-Christian:** Multiple organ systems affected, including skull base
 - Letterer-Siwe:** Most severe form, typically involving abdominal viscera

CLINICAL ISSUES

- Isolated thyroid involvement more likely in older patients
- Important to identify isolated thyroid disease vs. part of more widespread disease
- Prognosis closely related to extent of disease
 - Localized: Excellent; systemic: Aggressive, with poor prognosis

MICROSCOPIC

- Subcapsular and septal location more common
- Infiltrate frequently effaces thyroid architecture
- Collections of enlarged cells with delicate, pale, or eosinophilic cytoplasm surrounding vesicular nuclei
- Nuclei have indented, notched, lobulated, folded, grooved, or coffee bean shape
- Increased number of eosinophils

ANCILLARY TESTS

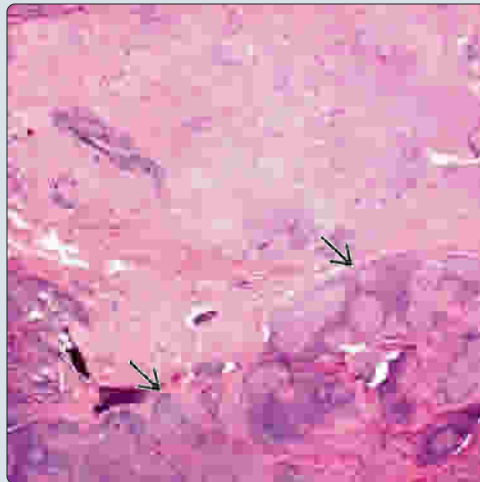
- Practical panel: S100 protein, CD1a, Langerin, CD68
- Invaginations of cell membranes (Birbeck granules)
 - Pentilaminar, with cross striations and vesicular expansions by electron microscopy

TOP DIFFERENTIAL DIAGNOSES

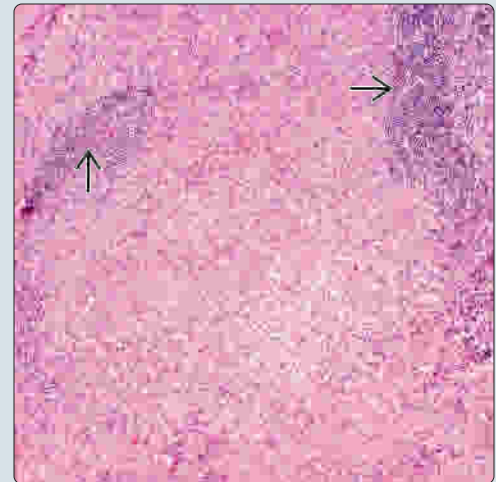
- Rosai-Dorfman disease, chronic lymphocytic thyroiditis, thyroid papillary carcinoma, undifferentiated carcinoma, infections

Single Focus of LCH

(Left) A single focus of Langerhans cell histiocytosis (LCH) is associated with lymphocytic thyroiditis [2]. The infiltrate has effaced the thyroid follicular architecture. There is associated fibrosis in this case. **(Right)** There is a collection of histiocytes, focally associated with lymphocytic thyroiditis [2]. There is a "lightness" to the focus, as the cytoplasm is foamy. Eosinophils can be seen.

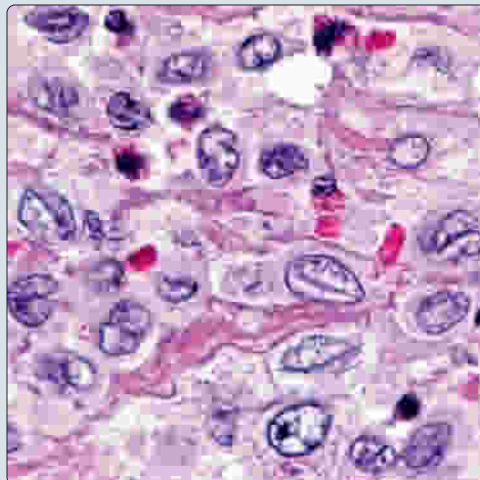


Nodule of Histiocytes With Eosinophils

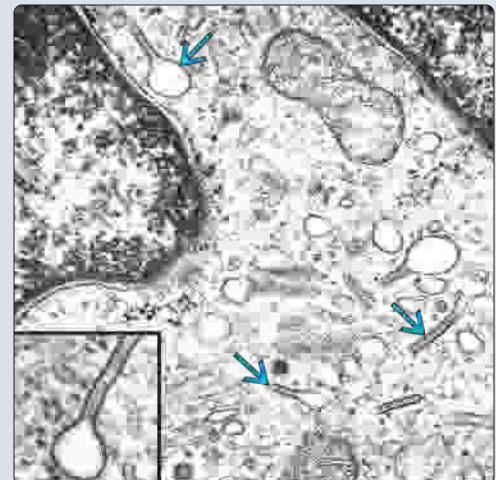


Nuclear Folds and Contour Irregularities

(Left) The nuclei have irregular folds and grooves, with small notches noted in this example of LCH. Isolated eosinophils are present in the background, a common finding for this diagnosis. **(Right)** The nucleus is folded and convoluted. Cell membrane invaginations result in disc-shaped granules that are rod-shaped [2] on cross section. These Birbeck or Langerhans granules are pentilaminar, with cross striations and vesicular expansions yielding a tennis racquet appearance (inset). (Courtesy S. Bhuta, MD.)



Birbeck Granules on EM



TERMINOLOGY

Abbreviations

- Langerhans cell histiocytosis (LCH)

Definitions

- Increased number of Langerhans cells: Unique histiocyte-containing Birbeck granules
- 3 distinct but interrelated clinical syndromes share identical histologic features
 - **Eosinophilic granuloma:** Predominantly osseous or pulmonary isolated disease
 - **Hand-Schüller-Christian:** Multiple organ systems affected, including skull base
 - **Letterer-Siwe:** Most severe form, typically involving abdominal viscera

ETIOLOGY/PATHOGENESIS

Etiology

- Although unknown, causes include neoplastic process or abnormal proliferative process

Pathogenesis

- Clonal disorder of Langerhans cells, believed to be modified histiocyte derived from dendritic system
 - *BRAF*V600E detected most consistently
- Misguided differentiation of myeloid dendritic cell precursors
 - Somatic mutations in *MAP2K1*-induced extracellular signal-regulated kinase phosphorylation (critical in myeloid differentiation)
- Somatic mutations of mitogen-activated protein kinase (MAPK) pathway genes *ARAF* and *ERBB3*

CLINICAL ISSUES

Epidemiology

- Incidence
 - Isolated disease is exceptionally rare
 - May be more frequent as part of systemic disease
- Age
 - Wide range: Birth to old age
 - Isolated thyroid involvement more likely in older patients
 - Systemic disease more likely at young age (< 20 years)
- Sex
 - Equal gender distribution

Site

- May be focal or diffuse thyroid involvement

Presentation

- Important to identify isolated thyroid disease vs. part of more widespread disease
- Usually presents with unilateral thyroid gland nodule
- Uncommonly, presents with sore throat, upper respiratory tract infection, skin rash, pulmonary distress, gastrointestinal symptoms, lymph node enlargement
 - Usually in patients with systemic involvement
 - Bone, skin, liver, lymph nodes, lungs, central nervous system, spleen, gastrointestinal tract
- Duration of symptoms varies based on disease

- Days: Systemic disease; years: Isolated disease

Treatment

- Options, risks, complications
 - Treatment differs for isolated/localized vs. systemic disease
 - Must exclude systemic disease
- Surgical approaches
 - Surgery is sufficient for localized thyroid disease
- Drugs
 - Combination chemotherapy for systemic disease
 - Targeted therapy with *BRAF* inhibitors shows promise

Prognosis

- Closely related to extent of disease
 - Localized: Excellent
 - Systemic disease: Aggressive, with poor prognosis
- When thyroid is primary presentation, subsequent systemic disease is rare

IMAGING

Radiographic Findings

- Scintigraphic studies show cold nodule
- Ultrasonography demonstrates mixed-density mass lesion

MACROSCOPIC

General Features

- Nodule, usually indistinguishable from other thyroid nodules

Size

- Range: 0.2-8.0 cm

MICROSCOPIC

Histologic Features

- Focal or diffuse thyroid gland involvement
 - May extend beyond thyroid capsule, resulting in adherence to surrounding soft tissue or skeletal muscle
- Subcapsular and septal location more common
- Infiltrate pushes or destroys thyroid parenchyma, frequently effacing thyroid follicular architecture
- Collections of enlarged cells with delicate, pale, or eosinophilic cytoplasm surrounding vesicular nuclei
- Nuclei have indented, notched, lobulated, folded, grooved, or coffee bean shape
- Cytoplasm is often finely vacuolated, with phagocytized cellular debris
- Increased number of eosinophils
 - Concentrated in collections around areas of necrosis
- Lymphocytic thyroiditis (Hashimoto thyroiditis) commonly present
- Adenomatoid nodules and thyroid papillary carcinoma may concurrently be present

ANCILLARY TESTS

Cytology

- Scant colloid in smears with high cellularity
- Isolated, discrete, atypical, large mononucleated cells
 - May be loosely aggregated

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
S100	Positive	Nuclear & cytoplasmic	All tumor cells are positive
CD1a	Positive	Cytoplasmic	Almost all lesional cells
CD207	Positive	Cytoplasmic	Langerin gives dot-like paranuclear positivity
CD68	Positive	Cytoplasmic	Almost all lesional cells
Lysozyme	Positive	Cytoplasmic	Most lesional cells
Fascin	Positive	Cytoplasmic	Variably positive, depending on maturation
CD15	Positive	Dot positivity	Highlights Golgi or perinuclear zone
CD30	Positive	Dot positivity	Ki-1 highlights Golgi or perinuclear zone
PLAP	Positive	Cytoplasmic	Many lesional cells reactive
CK-PAN	Negative		
TTF-1	Negative		
Thyroglobulin	Negative		

- Contorted nuclei with longitudinal nuclear folds/grooves
- Abundant, foamy granular cytoplasm
- Background of eosinophils, lymphocytes, and multinucleated and foamy histiocytes
- Mitotic figures are common

Immunohistochemistry

- Langerhans cells have wide immunohistochemistry panel
 - Macrophage antigens give concentration in perinuclear and Golgi regions
 - **Negative:** Cytokeratin, thyroglobulin, TTF-1
- Practical panel: S100 protein, CD1a, Langerin (CD207), CD68

Genetic Testing

- Most common recurrent mutation: *BRAF*V600E mutation
- Mutually exclusive somatic mutations in *MAP2K1* (encodes MEK1 protein)
- MAPK pathway genes *ARAF* and *ERBB3* may also be affected

Electron Microscopy

- Folded, convoluted, and lobulated nuclei
- Cytoplasmic filopodial extensions and invaginations
- Invaginations of cell membranes called Birbeck granules or Langerhans granules
 - Granules are disc-shaped, but on cross section they are rod-shaped
 - Pentilaminar, with cross striations and vesicular expansions
 - Tennis racquet appearance
 - Langerin (CD207) is protein that makes up Birbeck granules

DIFFERENTIAL DIAGNOSIS

Rosai-Dorfman Disease

- Massive lymphadenopathy with sinus histiocytosis has characteristic emperipolesis (phagocytized nuclear debris in cytoplasm of histiocyte)
- **Positive:** S100 protein; **negative:** CD207, CD1a
- Identified in perithyroidal lymph nodes (not thyroid gland)

Chronic Lymphocytic Thyroiditis

- When thyroiditis is extensive or heavy, histiocytes and eosinophils of LCH may be overlooked

Thyroid Papillary Carcinoma

- Cohesive clusters of epithelial cells with nuclear enlargement, nuclear chromatin clearing, nuclear grooves, and intranuclear cytoplasmic inclusions
- Eosinophils and histiocytes are absent

Undifferentiated Carcinoma

- Significant pleomorphism, extensive necrosis, lacks inflammatory infiltrate

Infections

- Thyroid gland may rarely be site of fungal or parasitic infections
- Eosinophils may be seen, but no CD1a- or CD207-reactive histiocytes

DIAGNOSTIC CHECKLIST

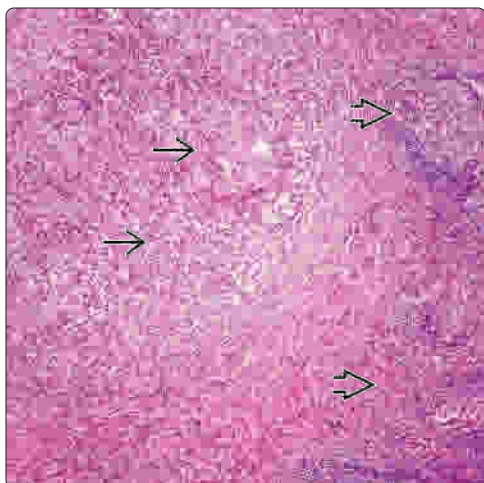
Clinically Relevant Pathologic Features

- Recognition should prompt exclusion of systemic disease

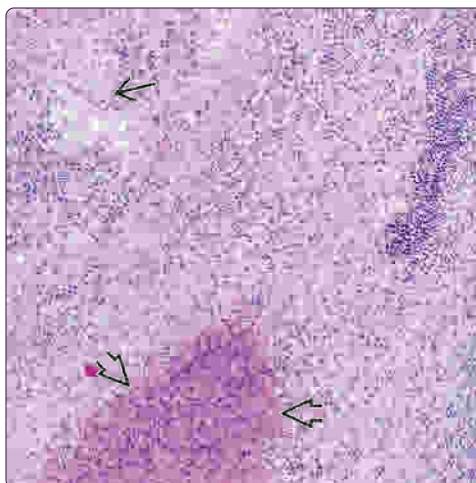
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1. Berres ML et al: Progress in understanding the pathogenesis of Langerhans cell histiocytosis: back to Histiocytosis X? *Br J Haematol.* 169(1):3-13, 2015
2. Demellawy DE et al: Langerhans cell histiocytosis: a comprehensive review. *Pathology.* 47(4):294-301, 2015
3. Moschovi M et al: Synchronous and metachronous thyroid cancer in relation to Langerhans cell histiocytosis: involvement of V600E BRAF-mutation? *Pediatr Blood Cancer.* 62(1):173-4, 2015
4. Pusztaszeri MP et al: Fine-needle aspiration of primary Langerhans cell histiocytosis of the thyroid gland, a potential mimic of papillary thyroid carcinoma. *Acta Cytol.* 57(4):406-12, 2013
5. Patten DK et al: Solitary langerhans histiocytosis of the thyroid gland: a case report and literature review. *Head Neck Pathol.* 6(2):279-89, 2012
6. Vergez S et al: Langerhans cell histiocytosis of the thyroid is a rare entity, but an association with a papillary thyroid carcinoma is often described. *Endocr Pathol.* 21(4):274-6, 2010
7. Elliott DD et al: Langerhans cell histiocytosis presenting as a thyroid gland mass. *Ann Diagn Pathol.* 9(5):267-74, 2005
8. Thompson LD: Langerhans cell histiocytosis isolated to the thyroid gland. *Eur Arch Otorhinolaryngol.* 253(1-2):62-5, 1996
9. Thompson LD et al: Langerhans cell histiocytosis of the thyroid: a series of seven cases and a review of the literature. *Mod Pathol.* 9(2):145-9, 1996

Destructive Growth of LCH

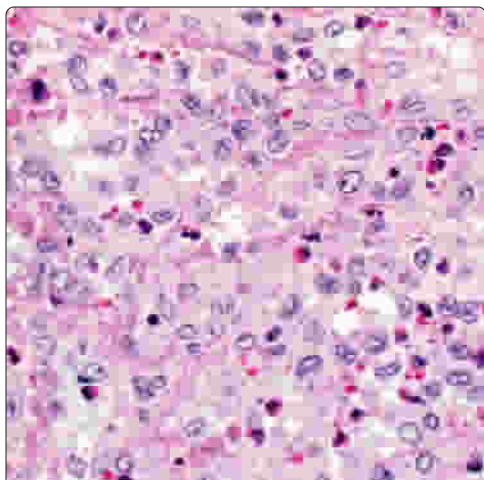


Pale Histiocytes With Eosinophils

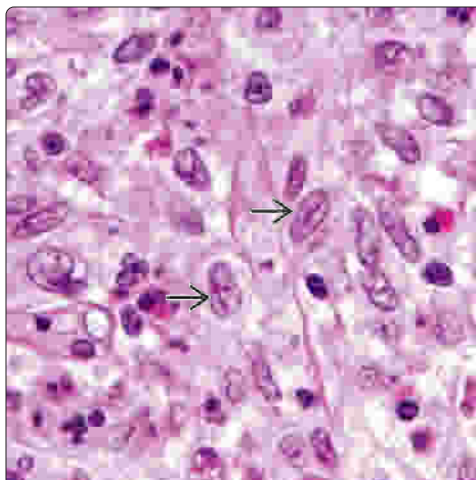


(Left) This focus of LCH is associated with an abscess formation, in which eosinophils form the abscess. The thyroid parenchyma is destroyed. There is chronic lymphocytic thyroiditis at the periphery. **(Right)** There are sheets of histiocytes associated with an area of abscess formation. Numerous eosinophils are noted. An isolated focus of residual thyroid gland tissue is seen.

Cleaved, Coffee Bean-Shaped Nuclei

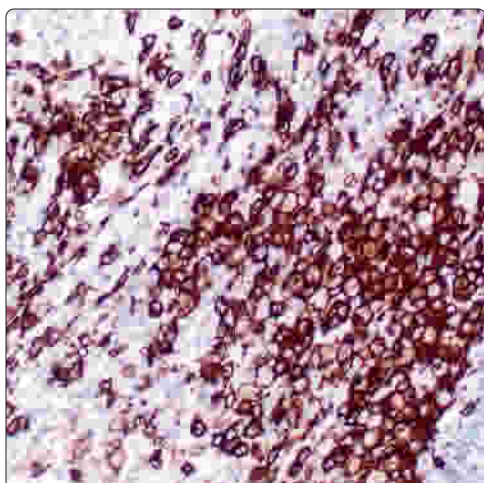


Sheets of Histiocytes With Folds/Cleaves

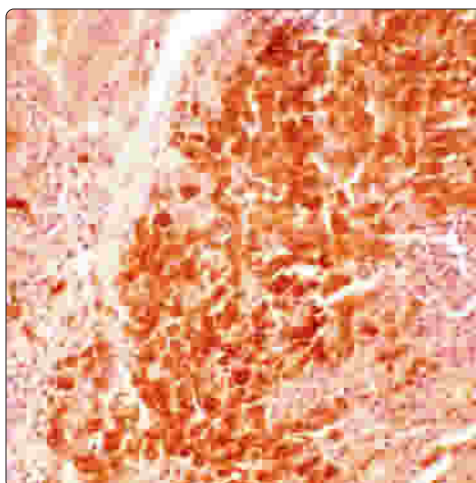


(Left) The Langerhans cells have abundant delicate, pale cytoplasm surrounding nuclei that have indented, notched, lobulated, folded, grooved, or coffee bean shape. Eosinophils are noted. **(Right)** The polyhedral to spindled cells have delicate, foamy cytoplasm surrounding indented or folded nuclei with longitudinal grooves, yielding a coffee bean shape. Note the increased number of eosinophils in the background.

Strong Cytoplasmic CD1a Reaction



Strong, Diffuse S100 Protein Reaction



(Left) There is a strong, cytoplasmic reaction of the Langerhans cells with CD1a. Several immunohistochemistry markers are positive, with Langerin (CD207) considered the most specific. **(Right)** Strong and diffuse nuclear and cytoplasmic S100 protein reactivity is noted in this collection of LCH. CD1a and CD68 would also give similar results, although only in the cytoplasm.

Ovarian Thyroid Tissue

KEY FACTS

TERMINOLOGY

- **Ovarian thyroid tissue**
 - Presence of thyroid parenchyma in setting of ovarian teratoma
 - Thyroid tissue represents only minor component of ovarian teratoma
- **Struma ovarii**
 - Ovarian teratomas in which thyroid tissue is predominant (at least 50%) or sole tissue component
- **Strumal carcinoid**
 - Ovarian tumor includes presence of thyroid tissue admixed with carcinoid tumor

CLINICAL ISSUES

- 5-15% of mature ovarian teratomas contain thyroid tissue
- Presentation is similar to ovarian teratoma
- Enlarging abdominal mass
- For struma ovarii, surgical removal is curative

- For strumal carcinoid, prognosis considered excellent following surgical removal even in presence of metastases
- Prognosis associated with malignant thyroid tumors in struma ovarii considered good, with overall survival rates of 89% at 10 years and 84% at 25 years

MICROSCOPIC

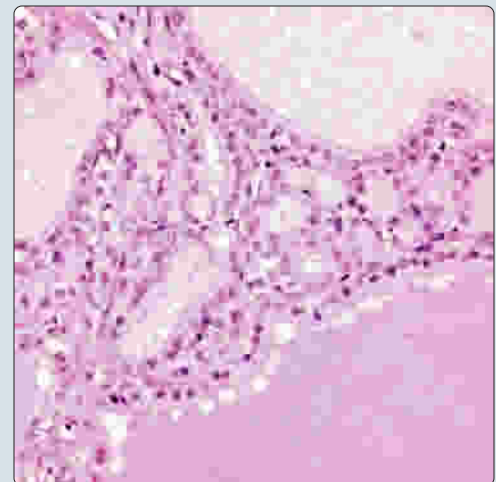
- **Struma ovarii**
 - Normal-appearing thyroid follicular tissue (most common finding)
 - Pathologic changes may include
 - Multinodular goiter
 - Rarely, thyroid neoplasms arise in struma ovarii including
 - Papillary thyroid carcinoma most common
 - Follicular carcinoma
- **Strumal carcinoid**
 - Characterized by presence of normal thyroid tissue admixed with carcinoid tumor

Thyroid Tissue in Teratoma

(Left) Thyroid tissue composed of colloid-filled follicles represented the minor component within ovarian parenchyma with findings of an ovarian teratoma (not shown). The thyroid tissue had changes of an adenomatoid nodule with associated retrogressive changes, including cyst formation. **(Right)** The thyroid tissue shows colloid-filled follicles composed of follicular epithelial cells with basally oriented, uniform-appearing, round nuclei with coarse nuclear chromatin.

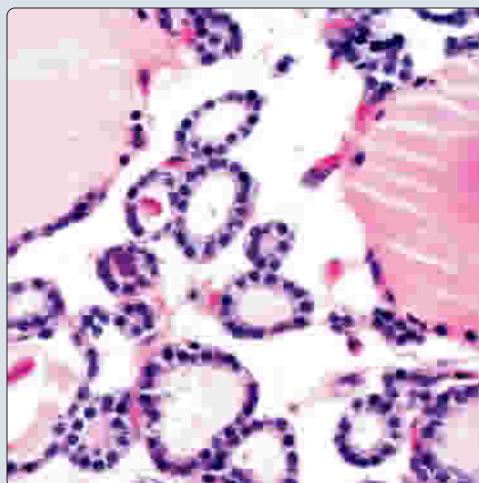


Thyroid Parenchyma



Bland Thyroid Gland Tissue

(Left) At higher magnification, the follicles are lined by bland-appearing nuclei lacking features associated with papillary thyroid carcinoma. The thyroid tissue was a part of changes associated with multinodular goiter (adenomatoid nodule). **(Right)** Papillary thyroid carcinoma in struma ovarii (malignant struma) is shown. At low magnification, colloid-filled thyroid follicles are present in ovarian parenchyma showing a follicular growth pattern.



Malignant Struma Ovarii



TERMINOLOGY**Definitions**

- **Ovarian thyroid tissue**
 - Presence of thyroid parenchyma in setting of ovarian teratoma
 - Thyroid tissue represents only minor component of ovarian teratoma
- **Struma ovarii**
 - Ovarian teratomas in which thyroid tissue is predominant (at least 50%) or sole tissue component
- **Strumal carcinoid**
 - Ovarian tumor includes presence of thyroid tissue admixed with carcinoid tumor
 - In this setting, other teratomatous elements usually absent

ETIOLOGY/PATHOGENESIS**Idiopathic**

- No known associated causes or risk factors

CLINICAL ISSUES**Epidemiology**

- Incidence
 - 5-15% of mature ovarian teratomas contain thyroid tissue
- Age
 - **Struma ovarii**
 - Occurs mainly over 40 years of age but may occur over wide range, including 2nd to 9th decades of life
 - **Strumal carcinoid**
 - Majority are postmenopausal but may occur over wide age range, from 3rd to 8th decades of life
- Sex
 - Exclusively in women

Site

- Exclusively limited to ovary; bilaterality may occur in up to 5% of cases

Presentation

- **Struma ovarii**
 - Presentation is similar to ovarian teratoma
 - Enlarging abdominal mass
 - Incidental finding on routine gynecologic (or urologic) evaluation
 - Other (uncommon) clinical presentations may include
 - Symptoms related to function of thyroid component (hyperthyroidism) in < 10%
 - Ascites that, in presence of ovarian mass, may be suspicious for ovarian carcinoma
 - Ascites and hydrothorax (pseudo-Meig syndrome) may occur
- **Strumal carcinoid**
 - Presentation similar to ovarian teratoma
 - Abdominal mass, acute abdominal pain
 - May be identified incidentally on routine gynecologic (or urologic) evaluation
 - Rarely, may initially be detected as ovarian mass complicating pregnancy

- Other uncommon presentations may include
 - Constipation (peptide YY found in association with constipation)
 - Pain on defecation
 - Virilization, hirsutism
 - Symptoms related to hyperthyroidism rarely occur
 - May be seen in multiple endocrine neoplasia 2A
- Carcinoid syndrome
 - Rare occurrence reported
 - May include facial flushing, diarrhea, bronchospasm, hypertension

Laboratory Tests

- **Struma ovarii**
 - Functional abnormalities may occur including
 - Hyperthyroidism (rarely struma ovarii may coexist with Graves disease)
 - Increased serum thyroglobulin may be present in metastatic thyroid carcinoma arising in struma ovarii
 - Increased serum CA 125 levels in pseudo-Meig syndrome (ascites and hydrothorax)

Treatment

- Options, risks, complications
 - **Struma ovarii**
 - Surgical excision is treatment of choice (as well as for malignant struma)
 - In presence of normally situated (cervical) thyroid gland without abnormalities, thyroidectomy not indicated
 - Treatment for metastatic papillary thyroid carcinoma in struma ovarii may include
 - Surgical removal ± supplemental radioactive iodine therapy
 - Use of radioactive iodine therapy would necessitate ablation of cervical thyroid gland
 - **Strumal carcinoid**
 - Unilateral salpingo-oophorectomy in younger aged patients
 - Bilateral oophorectomy and hysterectomy in older aged patients

Prognosis

- **Struma ovarii**
 - Surgical removal is curative
 - Prognosis associated with malignant thyroid tumors in struma ovarii considered good with overall survival rates of
 - 89% at 10 years
 - 84% at 25 years
 - Although unusual, fatalities secondary to widespread metastatic disease have occurred
- Metastatic disease from papillary carcinoma may occur
 - To contralateral ovary, peritoneum, regional lymph nodes, liver, and brain
- **Benign strumatosis**
 - Term utilized for presence of benign thyroid follicular epithelium within peritoneum
 - These foci should be considered as representing metastatic thyroid carcinoma
- Pathologic factors predictive of poorer prognosis include

- Large size (≥ 10 cm); strumal component $> 80\%$; extensive papillary carcinoma, especially with solid areas; necrosis, ≥ 5 mitoses per 10 HPF
- **Strumal carcinoid**
 - Prognosis considered excellent following surgical removal, even in presence of metastatic tumor
 - Both strumal and carcinoid components capable of giving rise to metastases

MACROSCOPIC

General Features

- **Struma ovarii**
 - Often resembles nodular goiter appearing as multiple glistening, brown nodules

MICROSCOPIC

Histologic Features

- **Struma ovarii**
 - Normal-appearing thyroid follicular tissue (most common finding)
 - Multinodular goiter with colloid-filled, variably sized follicles lined by flattened follicular epithelial cells
 - Secondary retrogressive changes (e.g., fibrosis, cyst formation, hemorrhage) may be present
 - Changes of lymphocytic thyroiditis may be present
 - Other less common findings
 - Papillary hyperplasia of follicular epithelium, clear cells, signet ring cells
 - **Proliferative struma ovarii**
 - Refers to discrete mass composed of densely cellular thyroid follicles (without evidence of malignancy)
- Rarely, thyroid neoplasms arise in setting of struma ovarii and when malignant referred to as malignant struma
 - Papillary thyroid carcinoma
 - Diagnosis based on cytomorphologic (i.e., nuclear) features
 - Most are conventional type and follicular variant; less commonly other variants reported including tall cell variant
 - Invasive growth (vascular or stromal) not required for diagnosis of papillary carcinoma
 - Follicular carcinoma
 - Diagnosis based on presence of capsular or vascular invasion
- **Strumal carcinoid**
 - Characterized by presence of normal thyroid tissue admixed with carcinoid tumor
 - Diagnosis made as long as both components are present, not on whether one or other predominates
 - Carcinoid component histologically identical with similar IHC staining to carcinoid tumors in other locations

ANCILLARY TESTS

Immunohistochemistry

- **Struma ovarii**
 - Thyroglobulin and TTF-1(+)
 - Calcitonin, chromogranin, synaptophysin negative
- **Strumal carcinoid**
 - Chromogranin, synaptophysin, CD56(+)

- Calcitonin only rarely found
- Thyroglobulin, TTF-1(-) in carcinoid component
- Neurohormonal peptides can be present: Pancreatic polypeptide, vasoactive intestinal polypeptide, insulin, glucagon, substance-P, somatostatin

Genetic Testing

- Various molecular alterations identified in malignant struma ovarii including *RET/PTCH1* or *NCOA4*, *BRAF*, *RAS*, *PAX8-PPARG*

DIFFERENTIAL DIAGNOSIS

Metastatic Thyroid Carcinoma to Ovary

- Extraordinarily rare occurrence
- In presence of malignant thyroid neoplasms in struma ovarii, detailed evaluation of thyroid gland proper indicated

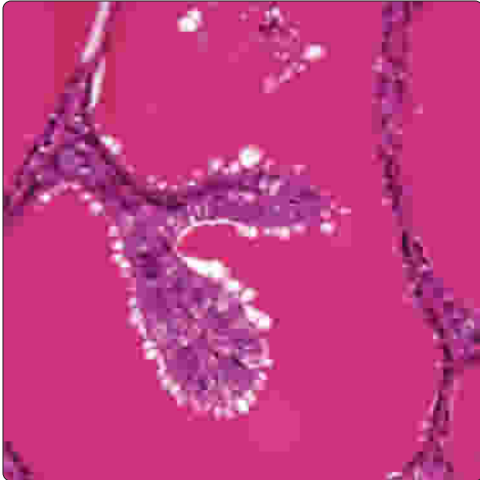
Metastatic Carcinoid to Ovary

- Common feature from gastrointestinal carcinoids (appendix, small intestine)
- Clues in support of metastasis to ovary include bilaterality, multinodularity, and presence of peritoneal metastases

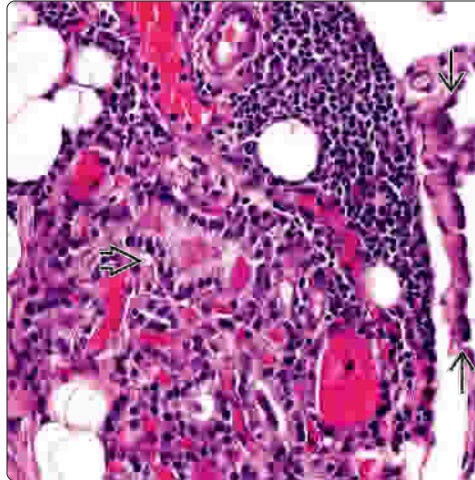
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Papillary Carcinoma

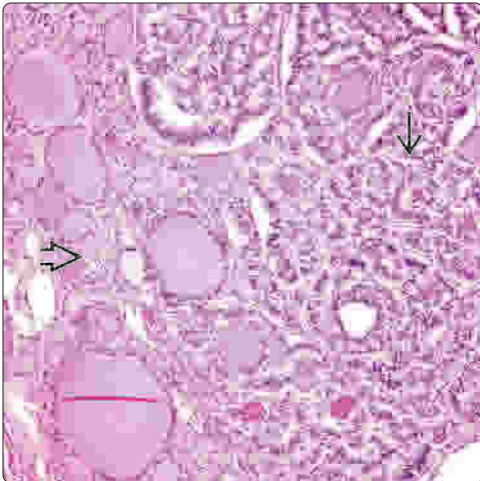


Metastatic Papillary Carcinoma

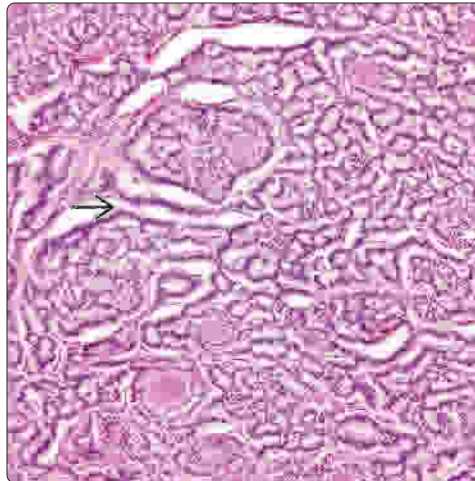


(Left) Areas of papillary architecture with fibrovascular core were present that, in conjunction with diagnostic nuclear features, allowed for the diagnosis of a classic type of papillary thyroid carcinoma in the setting of struma ovarii. (Right) In addition to the findings within the ovary of malignant struma, the papillary thyroid carcinoma was metastatic to a mesenteric lymph node; mesothelial cells are identified.

Thyroid With Carcinoid Tumor

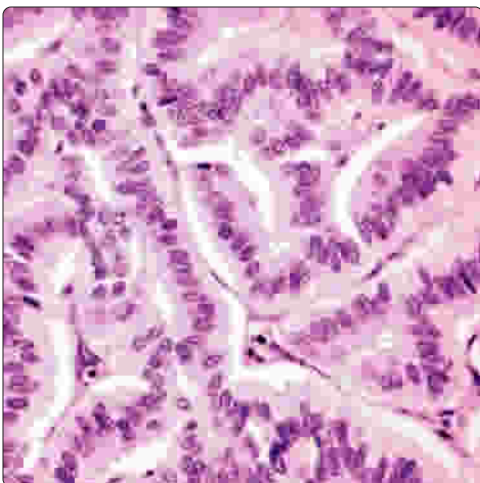


Strumal Carcinoid

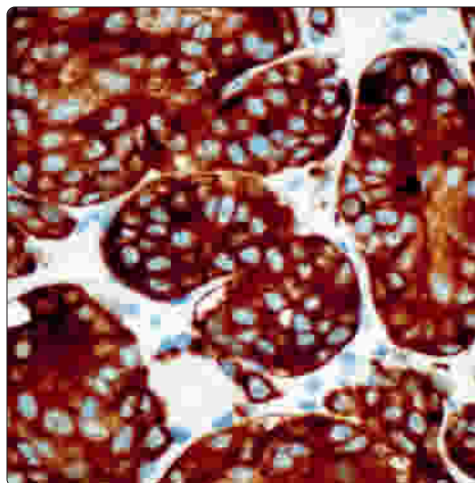


(Left) Strumal carcinoid includes an admixture of normal thyroid follicles and the carcinoid tumor characterized by trabecular and organoid growth, identical to features seen in carcinoid tumors of other sites. (Right) Strumal carcinoid shows a portion of the lesion entirely comprised of the carcinoid tumor characterized by complex growth, including trabecular pattern. The diagnosis is based on finding both components, irrespective of the amount of each component in any given neoplasm.

Bland Nuclei With NE Features



Strong Synaptophysin Reaction



(Left) The neoplastic cells in strumal carcinoid are identical to those seen in carcinoid tumors of more common sites, including relatively uniform-appearing cells with dispersed (salt and pepper) nuclear chromatin, absence of significant nuclear pleomorphism, and absence of increased mitotic activity. (Right) Confirmation of neuroendocrine differentiation in carcinoid tumor includes (but is not limited to) the presence of diffuse and strong synaptophysin staining.

KEY FACTS

CLINICAL ISSUES

- Accounts for vast majority (85%) of all malignant thyroid neoplasms
- Female >> male (4:1)
- Surgery is treatment of choice
- > 98% 20-year survival
- Age (> 45 years), size (> 2 cm), and gender (male) are most important

MACROSCOPIC

- Discrete, ill-defined mass with irregular or infiltrative border
- Gritty, dystrophic calcification is common

MICROSCOPIC

- Multiple different patterns in same tumor
 - Papillary, solid, trabecular, micro- or macrofollicular
- Complex, arborizing, delicate, narrow papillae
- Intratumor, sclerotic eosinophilic fibrosis
- Psammoma bodies

- Nuclear enlargement, overlapping, and crowding with high nuclear:cytoplasmic ratio
- Nuclear chromatin clearing, contour irregularities, nuclear grooves, intranuclear cytoplasmic inclusions
- Many variants, but most important: Follicular, macrofollicular, oncocytic, and microscopic

ANCILLARY TESTS

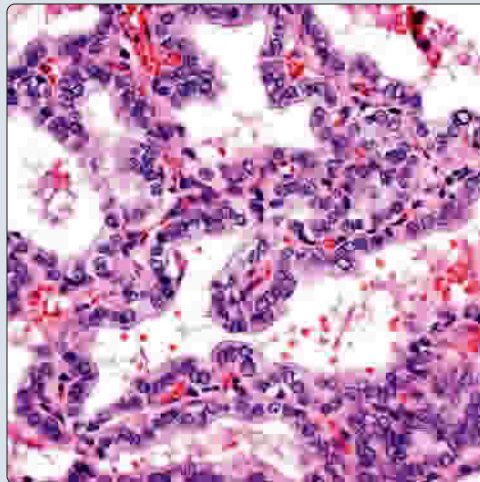
- Panel: HBME-1, galectin-3, MSG1 (CITED-1) is more sensitive and specific for thyroid papillary carcinoma (TPC)
- *BRAF* gene mutations are the most common genetic alterations in TPC

TOP DIFFERENTIAL DIAGNOSES

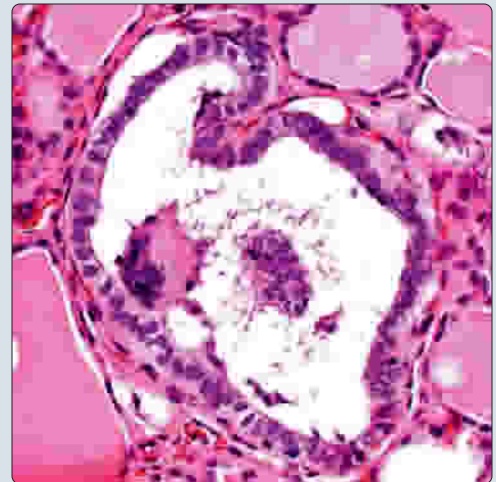
- Adenomatoid nodules, diffuse hyperplasia
- Noninvasive follicular thyroid neoplasm with papillary-like nuclei
- Follicular carcinoma, medullary carcinoma

Arborizing, Complex Papillae

(Left) There is an arborizing pattern of complex, irregular, ramifying, and overlapping papillae. The cells are enlarged and show nonpolar, haphazard nuclear position within the cell. Note the lack of colloid. **(Right)** Size variant (microscopic) papillary carcinoma range from 1 follicle up to 1 cm. Here is a single follicle papillary carcinoma showing all of the architectural and cytomorphonuclear features of papillary carcinoma.

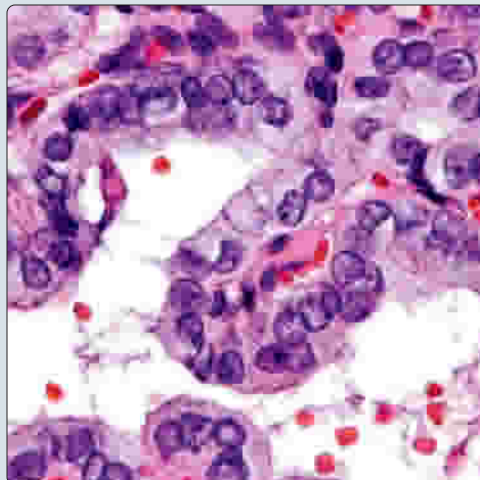


Microscopic Papillary Carcinoma

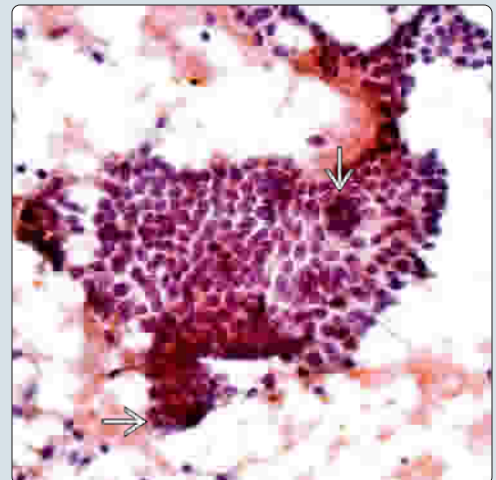


Nuclear Irregularities

(Left) This papillary structure is lined by irregular cells, showing demilune nuclei, nuclear grooves, and delicate, even nuclear chromatin distribution. Nucleoli are noted. There is irregular placement of the nuclei. **(Right)** A cellular smear with monolayered sheets (syncytium) focally shows 3D clusters of enlarged cells. The nuclei are enlarged with overlapping and irregular borders.



Monolayer With 3D Clusters



TERMINOLOGY

Abbreviations

- Thyroid papillary carcinoma (TPC)
- Papillary thyroid carcinoma (PTC)

Definitions

- Malignant epithelial tumor showing evidence of follicular cell differentiation and characterized by distinctive nuclear features

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Ionizing radiation exposure
 - Especially well-established relationship if exposure is in childhood
 - Chernobyl accident well studied and characterized tumor types: > 95% were PTC; no tall cell or columnar variants identified
 - Especially in solid variant of TPC
- Iodine-rich diet
 - Higher incidence of tumor in regions with high dietary iodine intake (Iceland, Japan)

Preexisting Benign Thyroid Disease

- Nodules associated with 6x increased risk
- Solitary nodule associated with 28x increased risk

Hereditary

- 5-10x increased risk in 1st-degree relatives of patients with papillary carcinoma
- ~ 5% of papillary carcinomas are familial
 - Familial adenomatous polyposis (FAP): *APC* gene germline mutations
 - Carney complex; Cowden syndrome (6% have PTC); PTEN-hamartoma tumor syndrome
 - Pure familial PTC (fPTC), fPTC associated with papillary renal cell carcinoma, and fPTC with multinodular goiter

Pathogenesis

- Monoclonal origin, with multifocal disease frequent

CLINICAL ISSUES

Epidemiology

- Incidence
 - Accounts for vast majority (85%) of all malignant thyroid neoplasms
 - 7.9/100,000 population
- Age
 - Usually young to middle-aged adults
 - 20-40 years for women
 - 40-60 years for men
 - Most common pediatric thyroid malignancy, although still uncommon
- Sex
 - Female > > male (4:1)
- Ethnicity
 - Whites > blacks

Presentation

- Solitary, painless thyroid mass

- Cervical lymphadenopathy (metastatic disease) may be present (~ 30%)
- Dysphagia, stridor, cough: More often in patients with large tumors (compression symptoms)
- Incidental tumors found during work-up for unrelated issues

Laboratory Tests

- Usually euthyroid
- Rare cases of hyper- or hypofunctional status
- Serum thyroglobulin can be used to monitor disease status (if elevated)

Natural History

- 20% prevalence of TPC at autopsy suggests indolent, nonaggressive tumors

Treatment

- Options, risks, complications
 - Recurrent laryngeal nerve damage and hypoparathyroidism are known complications
- Surgical approaches
 - Surgery is treatment of choice, although extent of surgery (lobectomy, subtotal thyroidectomy, or total thyroidectomy) remains controversial
 - Open vs. robotic-assisted total thyroidectomy (RATT): RATT associated with fewer lymph nodes retrieved and less-complete thyroid resection
 - Lymph node sampling generally only advocated if clinical or radiographic enlargement
 - Associated with increased risk of hypoparathyroidism
- Radiation
 - Radioablative iodine therapy is incorporated after total thyroidectomy
 - Tumor needs to show uptake of radiolabel to be therapeutically sensitive

Prognosis

- Excellent long-term clinical outcome
 - > 98% 20-year survival with < 0.2% mortality
 - Incidental, microscopic tumors (≤ 1 cm) show 0.5% recurrence rate
- Spreads preferentially by lymphatic channels
 - Intraglandular spread or metastases to regional lymph nodes
- Risk factors that influence recurrence
 - Age (> 45 years), size (> 2 cm), and gender (male) are most important
 - Extrathyroidal extension, lymph node metastases, and distant metastases also correlate but not as strongly
- *RET/NCOA4* and *TERT*(+) papillary carcinomas tend to have slightly worse prognosis, while *BRAF* status may influence management

IMAGING

Radiographic Findings

- MR scans are valuable in highlighting enlarged, cystic lymph nodes, help in identifying substernal lesions, and may define extrathyroidal extension
- MR scan shows increased signal intensity on T1-weighted images and may reveal punctate calcifications

Papillary Carcinoma

- Radioisotope scans typically reveal "cold" nodule but are no longer used

Ultrasonographic Findings

- Valuable guide for fine-needle aspiration (FNA)
- Defines size and shows if lesion is solid or cystic
- Hypoechoic or isoechoic solid nodule with ill-defined margins
- Cystic change can be seen
- Punctate microcalcifications (psammoma bodies) are frequent in papillary carcinoma
- High central blood flow within nodule on color Doppler is common in papillary carcinoma

MACROSCOPIC

General Features

- Discrete, ill-defined but circumscribed mass with irregular or infiltrative border
- Gritty, dystrophic calcification is common
- Extension beyond thyroid gland capsule or into adjacent thyroid parenchyma can be seen
- Cystic change is common
- Multifocality can be identified
- Cut surface is tan-brown, gray-white
- Papillary structures give shaggy texture
- Irregular areas of fibrosis are seen and must be sampled
- Lymph nodes may contain cysts filled with hemorrhagic, brownish fluid

Sections to Be Submitted

- Must be from tumor-to-capsule-to-parenchyma interface
- Generally, 1 section per cm of tumor size
 - However, center of tumor is not as important as periphery

Size

- Wide range; from microscopic to 20 cm
- Mean: 1-3 cm

MICROSCOPIC

Histologic Features

- Diagnostic features include growth pattern, nuclear features, psammoma bodies, and tumor fibrosis, **but** only nuclear features are required for diagnosis
 - No single feature is diagnostic
- Typically shows infiltrative growth with irregular, invasive border
- Multinodular and multifocal tumors are common
- Architectural features
 - Multiple different patterns in same tumor
 - Variable growth patterns: Papillary, solid, trabecular, micro- or macrofollicular, cystic
 - Elongated &/or twisted follicles
 - Complex, arborizing, ramifying, branching, delicate, narrow papillae
 - Finger-like projections composed of delicate fibrovascular cores covered by epithelial cells
 - Single layer of epithelial cells with nonpolar, haphazard (up and down) position of nucleus within cell

- May have loose myxoid, edematous, or hyalinized stroma
- Lymphoid cells can be seen within papillae
- Intratumor, acellular, sclerotic, dense, eosinophilic fibrosis
 - Generally found in 50-90% of all cases
 - Sometimes associated with irregular stellate fibrosis extending beyond tumor
 - Helpful at time of gross examination to determine areas to sample
 - Fibrosis is present in FV-PTC
- Mummification (peripheral cell death) very characteristic but infrequently seen
- Bright, hypereosinophilic, intense colloid (distinct from surrounding thyroid parenchyma)
- Psammoma bodies
 - Present in up to 50% of cases
 - Generally round/spherical shape
 - Represent apoptotic cells that form nidus for concentric lamellation/layers of calcium
 - Tombstone of previously viable tumor cell
 - Located in association with tumor cells, in tumor stroma, or in lymphatic channel
 - Often identified within lymph-vascular channels, diagnostic of intraglandular spread
 - Inspissated and calcified colloid in lumen is different
- Crystals can be seen in colloid
- Squamous metaplasia (~ 20% of cases), cyst formation, and degeneration are present, along with infarction
- Giant cells in colloid
- Chronic lymphocytic thyroiditis can be seen

Cytologic Features

- Large tumor cell size in comparison to surrounding tissue with high nuclear:cytoplasmic ratio
- Nuclear enlargement: 2-3x larger than nonneoplastic epithelium
- Nuclear overlapping and crowding: Haphazard arrangement, nuclei lack polarity, crowd out each another to give herd, lake, or egg basket appearance
 - Cellular overlapping and multilayering is not fixation or section thickness issue
- Chromatin clearing: Cleared chromatin with aggregation along nuclear membrane yielding accentuated nuclear membranes
 - Empty, pale, clear, ground-glass, or Orphan Annie eye nuclei
 - Tissue fixation is required, since clearing is not seen in frozen sections or FNA smears
 - Formalin fixation gives this clearing, but alcohol fixatives (SafeFix, HistoChoice) do not
 - May be related to heat: Sections placed on heating block before staining show this change to greater degree
- Irregularity of nuclear contours: Oval, elongated nucleus with asymmetric, angulated, crescent moon, convoluted, and triangular shapes, and highly irregular, jagged, rat bites into nuclear membrane
 - Do not assess in tissue previously frozen
- Nuclear grooves: Discrete, longitudinal folds through long axis of nucleus
 - Linear and regular (coffee bean)

- Curved and irregular (popcorn)
- Nuclear pseudo-inclusion: Invaginations of nuclear membrane pulling cytoplasm into nucleus
 - Rounded area within nucleus containing cytoplasmic material, sharply demarcated by thick nuclear membrane
 - Least frequently seen of nuclear features, but fixation artifacts may give this appearance in all cells, which should be discounted
 - Fixation vacuoles have empty, structureless appearance without rim of nuclear membrane
 - Nucleolus within vacuole shows it is not true pseudo-inclusion
- High nuclear:cytoplasmic ratio
- Nucleoli: If present, seem to touch nuclear membrane rather than being centrally located
- Cytoplasmic appearance is not helpful, except for oncocytic and clear variants

Lymphatic/Vascular Invasion

- Present in many cases, lymphatics preferentially

Margins

- Must assess to exclude extrathyroidal extension

Lymph Nodes

- Frequently show metastatic disease but should be stratified based on clinically apparent disease vs. microscopic disease and whether there is extranodal extension present
- Psammoma bodies represent metastasis
- Benign inclusions do not exist and should be considered metastatic carcinoma (lateral to sternocleidomastoid muscle)

Variants

- **Size variant (microscopic)**
 - a.k.a. microscopic, incidental, occult, or microcarcinoma
 - By definition, any TPC or variant can be ≤ 1 cm in size
 - Proclivity for subcapsular region
 - Frequently sclerotic with radiating scar-like infiltrating edge
 - Must be separated from intraglandular spread (intravascular; lacks capsule; has stellate, infiltrative growth)
 - No additional therapy is necessary for tumors of this size (significant controversy exists)
- **Follicular variant**
 - Usually encapsulated
 - Exclusively composed of small, tight follicles
 - Scant, hypereosinophilic colloid
 - Papillae are absent or vanishingly rare
 - Nuclei are large with pale to powdery to cleared nuclear chromatin, nuclear grooves, and inclusions
 - Internal tumor sclerosis or fibrosis is very helpful
- **Macrofollicular variant**
 - Most difficult to recognize
 - Architectural resemblance to adenomatoid or hyperplastic nodules
 - Predominantly large/macrofollicles with subtle increased cellularity, often accentuated at periphery
 - Colloid is often scalloped or vacuolated (like Graves)
 - Nuclei are flattened and hyperchromatic with isolated classic nuclei

- Abortive, rigid or straight papillary structures extend into center of colloid-filled follicle

- **Oncocytic variant**

- Macroscopically deep mahogany brown, frequently cystic
- $> 38\%$ of tumor should have complex, arborizing papillary structures
- Enlarged cells with abundant oncocytic (oxyphilic, Askanazy, Hürthle) cytoplasm
 - Cytoplasm is compact and glassy (increased mitochondria)
- Enlarged nuclei tend to be apically oriented
- Nuclei are slightly more hyperchromatic
- Numerous intranuclear cytoplasmic inclusions
- Positive with CK19
- Oncocytic cells can be seen in tall cell variant

- **Clear cell variant**

- Very uncommon variant
- Cells with clear cytoplasm
- Mixture of oncocytic and clear cells may be seen
- Must be distinguished from metastatic renal cell carcinoma or medullary carcinoma

- **Diffuse sclerosing variant**

- Young patients (mean: 18 years)
- Diffuse involvement of 1 or both lobes with nearly 100% of patients demonstrating cervical lymph node metastasis at time of presentation
- Firm gland with white streaks and gritty cut consistency
- Exaggerated papillary carcinoma
 - Extensive fibrosis, innumerable psammoma bodies, extensive intravascular and extrathyroidal extension, florid squamous metaplasia, dense lymphocytic thyroiditis
- Total thyroidectomy, lymph node dissection, and radioablative therapy gives excellent long-term prognosis

- **Columnar variant**

- Prominent papillary growth with markedly elongated, parallel follicles (railroad tracks)
- Scant colloid
- Tall cells with syncytial arrangement
- Prominent nuclear stratification of elongated nuclei with coarse and heavy chromatin deposition (distinctive)
- Subnuclear or supranuclear vacuolization of cytoplasm
- Squamous metaplasia in form of morules is common (endometrioid pattern)
- Mitotic figures may be present, along with necrosis

- **Tall cell variant**

- Tend to be older patients, more men, larger tumors (> 5 cm)
- Usually have extrathyroidal extension and increased incidence of metastases
- $> 70\%$ of tumor area must be tall cell
 - Tall cell: At least 3x as high as it is wide (plane of section must be taken into consideration)
- Papillary structures and elongated parallel follicles with scant/absent colloid
- Many intranuclear cytoplasmic inclusions and nuclear grooves
- Intercellular borders are sharply demarcated
- Nuclei are centrally located

- **Insular-solid variant**
 - Solid or insular pattern
 - Oval nests or islands with scant colloid
 - Cells with high nuclear:cytoplasmic ratio
 - Nuclear features of papillary carcinoma
- **Cribriform-morula variant**
 - Seen in patients with familial FAP
 - Diagnosis should prompt colonic exam and possibly genetic testing for germline *APC* mutation
 - *APC* mutations result in inappropriate activation of Wnt pathway results in accumulation of β -catenin in nucleus
 - Multiple well-demarcated or encapsulated tumor nodules
 - Mixed patterns of growth: Cribriform, trabecular, solid, papillary, and follicular
 - Whorls or morules composed of spindle cells without keratinization
 - Classic nuclear features of TPC are rare
 - **Positive:** Nuclear β -catenin, estrogen receptor, cyclin-D1; variable TTF-1, thyroglobulin
- **Hobnail variant**
 - Rare variant (~ 0.3%), female > male (2.2:1), older mean age (55 years), and larger tumors (> 3 cm)
 - Micropapillary structures, loss of polarity, with cuboidal cells showing high nuclear:cytoplasmic ratio, and apically placed nuclei, yielding surface bulge (apocrine snout) or hobnail appearance, along with single detached cells
 - High frequency of p53 overexpression; *BRAF* (V600E) usually present
 - Frequent extrathyroidal extension, lymphovascular invasion; less commonly tracheal invasion, tumor necrosis
 - Hobnail pattern in as little as 10% of tumor associated with worse prognosis
- **PTC with fasciitis-like stroma**
 - Features of papillary carcinoma blend with abundant cellular stroma resembling nodular fasciitis
- **Warthin-like variant**
 - Papillary carcinoma with lymphoid stroma

ANCILLARY TESTS

Cytology

- FNA is initial test of choice for thyroid nodule, with excellent sensitivity, specificity, and positive predictive value
- 25-gauge needle without suction yields excellent material uncontaminated by blood
- Adequacy: At least 6 groups of follicular cells with > 10 follicular cells per group
- Benign, indeterminate/suspicious, or malignant categories
- Cellular smears with monolayered sheets (syncytium)
- 3D clusters of enlarged cells
- Nuclei are enlarged, overlap, and have irregular borders
- Powdery/dusty, delicate nuclear chromatin on alcohol-fixed preparations
- Nuclear folds or grooves and intranuclear cytoplasmic inclusions are also common
- Colloid is thickened (chewing gum or ropy)
- Rarely psammoma bodies will be seen

Frozen Sections

- With preoperative FNA results, use of frozen section has decreased dramatically
- Only perform frozen section if FNA was suspicious for papillary carcinoma
- Diagnostic confirmation is possible, but follicular variant, thyroid papillary carcinoma (FV-TPC) is still difficult

Immunohistochemistry

- Seldom of value
 - May help define thyroid origin
 - May help define malignancy (in a few cases)
- Strongly and diffusely immunoreactive with keratin, CK7, thyroglobulin, TTF-1, CK19, HBME-1, galectin-3, MSG1 (CITED-1)
- Panel approach: HBME-1, galectin-3, MSG1 (CITED-1) may be more sensitive and specific for TPC

Genetic Testing

- Dependent on technique, immunohistochemistry, in situ hybridization, whether in adults or children, radiation history, and histologic variant
- Mitogen-activated protein kinase (MAPK) pathway regulates cell growth, differentiation, and survival
 - Activation of this pathway by either point mutation in *BRAF* and *RAS* genes or chromosomal rearrangement involving *RET* and *NTRK1* genes
 - Each specific mutation/rearrangement has unique effect due to distinct phenotypical and biological properties
- Point mutations of *BRAF* gene is most common genetic alteration in papillary carcinoma
 - T to A transversion at nucleotide 1799, which results in valine-to-glutamate substitution at residue 600 (V600E)
 - Mutations lead to constitutive activation of *BRAF* kinase, resulting in continuous stimulation of MEK, ERK, and subsequent downstream effectors of MAPK pathway
 - Correlated with histologic features: extra-thyroidal extension, advanced TNM stage, lymph node metastasis, multifocality and recurrence
- *RET/PTCH1* or *RET/NCOA4* fusion
 - Inversion inv(10)(q11.2;q21), which leads to *RET/PTCH1* rearrangement
 - Translocations or inversions involving 10q11.2 (*RET* gene region), correspond to less frequent types of *RET*/or rearrangements
- *RAS* mutations are seen in up to 15% of tumors
 - Found almost exclusively in FV-TPC, in tumors that are encapsulated, and tumors with low rate of lymph node metastases
 - Mutations are located at several specific sites (codons 12, 13, and 61) of *NRAS*, *HRAS*, and *KRAS* genes
 - Mutations stabilize protein in its active, guanosine triphosphate-bound conformation
 - Results in chronic stimulation of several signaling pathways, most importantly the MAPK and *PIK3CA/AKT1* pathways
- *EIF1AX*, *PPM1D*, and *CHEK2* are uncommon driver alterations
- *PTEN*, *PIK3CA*, and *AKT1* mutations (part of phosphoinositide 3-kinase [PI3K] pathway) are seen at low frequency

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
Galectin-3	Positive	Nuclear & cytoplasmic	Nearly all classic papillary carcinomas; important to have nuclear and cytoplasmic reactivity; not unique to thyroid papillary carcinoma (TPC)
HBME-1	Positive	Cell membrane & cytoplasm	Accentuated on apical surface; also stains colloid; more specific than galectin-3
MSG1	Positive	Nuclear & cytoplasmic	Equivalent to MSG1 (CITED-1); should be used as part of a panel: Galectin-3, HBME-1, and MSG1 (CITED-1)
TTF-1	Positive	Nuclear	All nuclei usually strong and diffusely positive
Thyroglobulin	Positive	Cytoplasmic	Accentuated at luminal surface and also in colloid; diffusion artifact a problem
CK19	Positive	Cell membrane & cytoplasm	Low specificity for TPC
pax-8	Positive	Nuclear	While strong reaction, background follicular cells are also positive
CK7	Positive	Cytoplasmic	Nearly all cells
CK8/18/CAM5.2	Positive	Cytoplasmic	Nearly all cells
CK-PAN	Positive	Cytoplasmic	Nearly all cells
NAPSIN-A	Positive	Cell membrane and cytoplasm	Tall cell variant specifically
ret	Positive		Very poor correlation with <i>RET/PTC</i> rearrangements
S100-A4	Positive	Cytoplasmic	Very limited utility
Calcitonin	Negative		
CK20	Negative		

- *TERT* promoter mutations (9%) strongly associated with high risk of recurrence (including *BRAF* mutated tumors) and less-differentiated tumors
- *NTRK1*, *ALK*, *MET*, *FGFR2*, and *THADA* fusions are seen infrequently

DIFFERENTIAL DIAGNOSIS

Adenomatoid Nodules

- Multiple nodules in general, lacking capsule
- Papillae are short, simple, nonbranching, and often thick
- Nuclei are round, regular, basally located, and hyperchromatic
- Intracytoplasmic hemosiderin pigment is usually lacking in PTC
- Qualitative and quantitative lack of nuclear features of PTC
- Alcohol fixatives will often cause nuclear enlargement and optical clearing

Diffuse Hyperplasia

- Whole gland affected (even if unevenly)
- Papillary structures are short, simple, nonbranching, and lined by single, polarized cell layer
- No nuclear features of papillary carcinoma (basal, round, hyperchromatic nuclei)

Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclei

- Nuclear features of PTC, but **noninvasive** with partial to completely encapsulated neoplasm

Follicular Carcinoma

- Oncocytic cytoplasm may induce nuclear enlargement
- Follicular architecture should predominate (i.e., no papillary structures)
- No nuclear features of papillary carcinoma

Medullary Carcinoma

- Follicular pattern, invasive growth, and **no** colloid
- Intranuclear cytoplasmic inclusions can be seen
- **Positive:** Calcitonin, chromogranin, CEA, TTF-1; **negative:** Thyroglobulin





DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

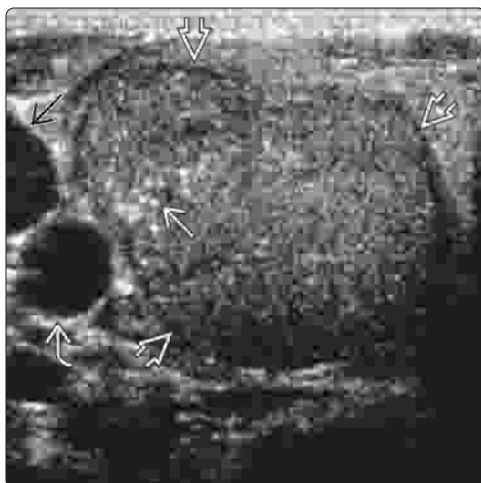
- Papillary carcinoma is almost always there; keep looking
- Default diagnosis is papillary carcinoma; prove it is not
- **No colloid:** Always think of medullary carcinoma, uncommon variants of papillary carcinoma, undifferentiated carcinoma, nonepithelial tumors, paraganglioma, lymphoma, etc.

SELECTED REFERENCES

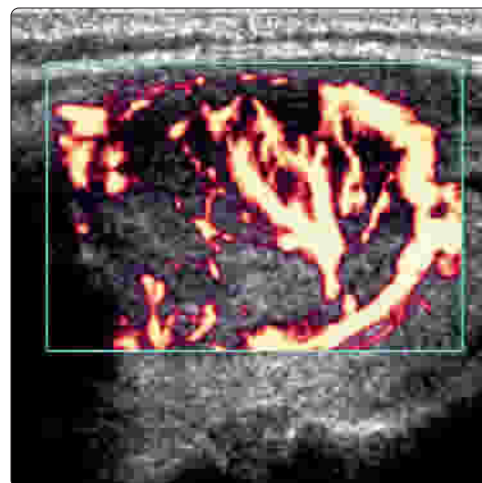
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


(Left) Transverse grayscale ultrasound shows a partially haloed , solid, hypoechoic thyroid nodule. The halo represents the capsule. There are numerous punctate calcifications , which represent psammoma bodies. The carotid artery  and internal jugular vein  are immediately adjacent. **(Right)** Corresponding power Doppler ultrasound shows profuse, chaotic intratumoral vascularity. This feature is more frequently seen in neoplasms than in adenomatoid nodules.

Ultrasound With Psammoma Bodies

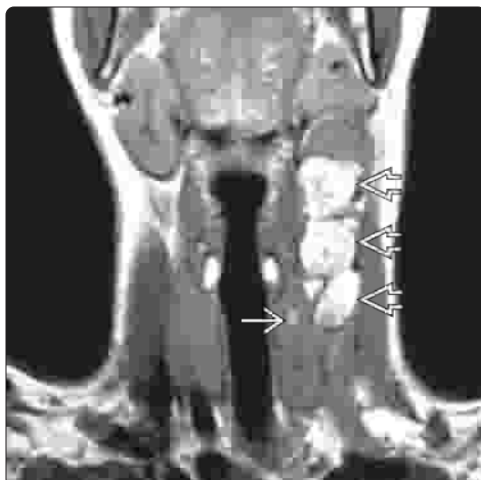


Doppler Ultrasound With Chaotic Vascular Flow

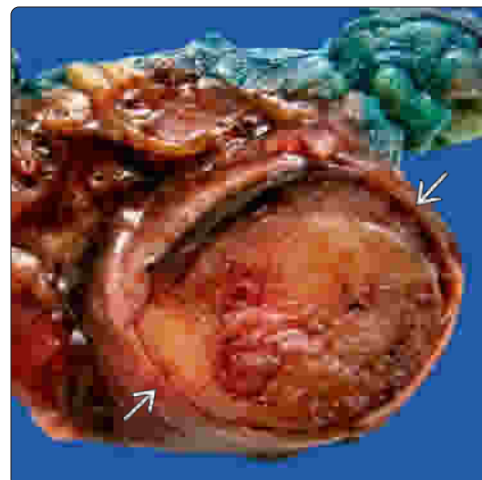



(Left) MR shows a < 0.5 cm hyperintense papillary carcinoma . Much larger and more easily identified are the characteristic hyperintense metastases to the deep cervical lymph nodes . Size disparity between the primary and metastases is common. **(Right)** There is a well-formed capsule  surrounding the tumor lacking areas of infiltration. There are numerous papillary projections giving a pebbled appearance. Papillary structures are frequently identified macroscopically in papillary carcinoma.

MR of Lymph Node Metastases

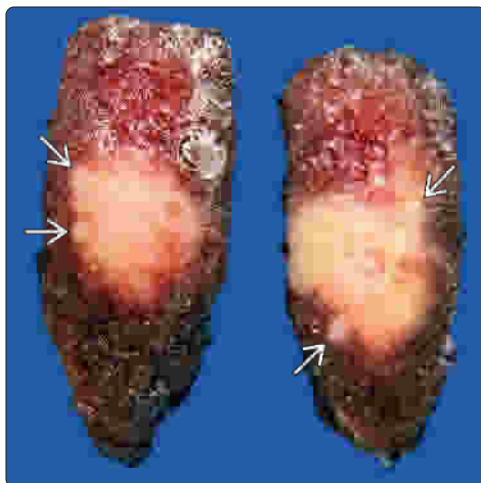


Encapsulated Papillary Carcinoma

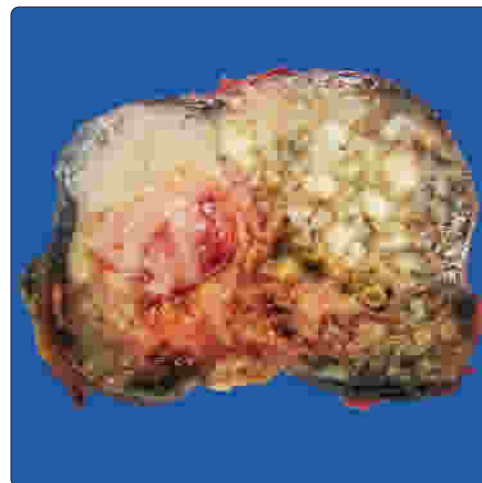


(Left) Gross photograph shows the characteristic irregular, sclerotic, light tan appearance of a papillary carcinoma. Note the small areas of invasion . The thyroid parenchyma is distinctly different in appearance from the tumor. **(Right)** There are multiple appearances to this tumor, with an irregular border, areas of necrosis and hemorrhage, and pale areas. This represented a columnar variant papillary thyroid carcinoma (PTC).

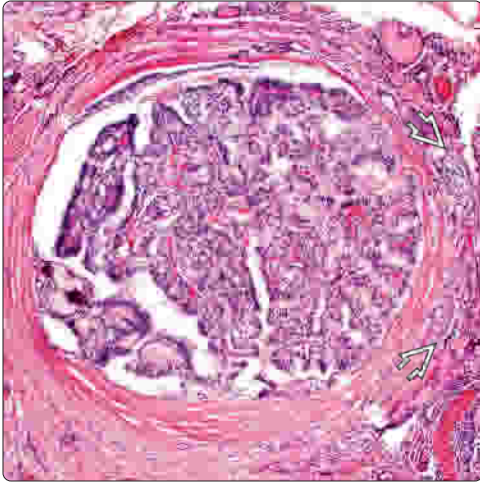
Irregular Sclerotic Infiltration



Fleshy, Irregular Nodular Tumor





Encapsulated Tumor With Invasion

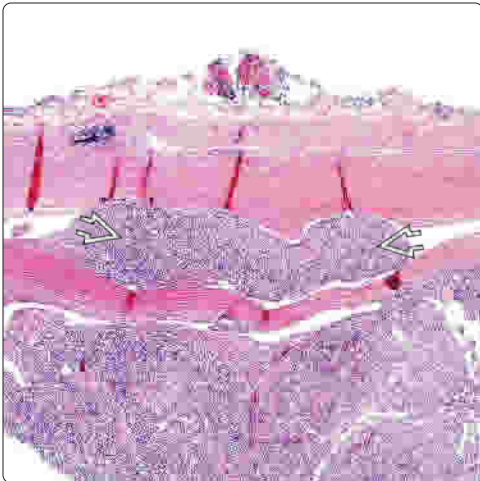


Frozen Section Showing Invasion

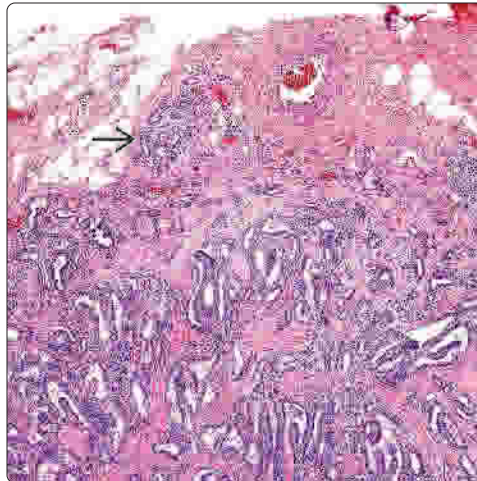




(Left) This tumor is surrounded by a well-formed fibrous connective capsule in which there are 2 areas of capsular invasion . Invasion qualifies the tumor as a carcinoma, which can then be further classified into a specific type, classical in this case. (Right) By chance, the frozen section captured an area of invasion  in this papillary carcinoma. There is a perpendicular tumor penetration through the capsule.

Vascular Invasion

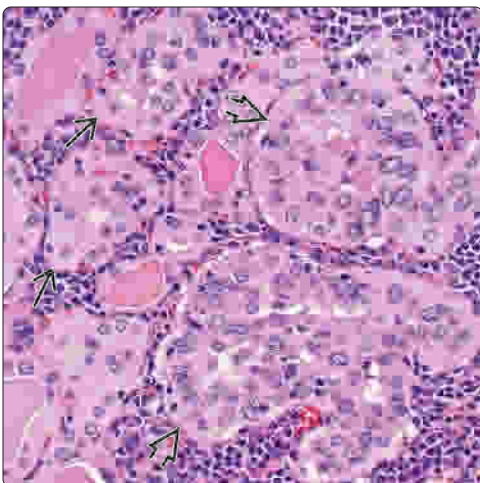


Extracapsular Extension

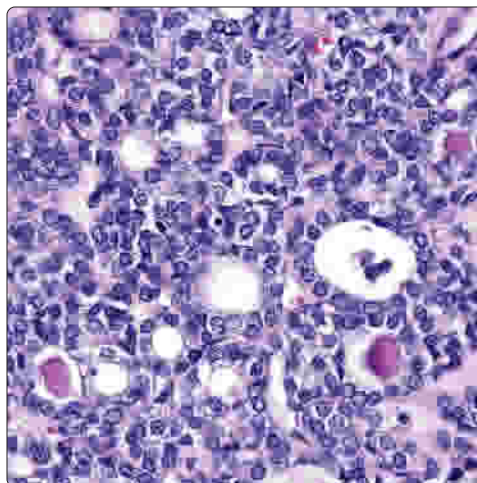




(Left) An area of vascular invasion  identified as a thrombus of tumor within a capsular vessel of this tumor is shown. Capsular and vascular invasions are frequently present, but encapsulated tumors may lack these features, while still representing papillary carcinoma. (Right) Tumor is present within extrathyroidal adipose tissue , adjacent to large vessels. Fat, nerves, and large vessels help to define the periphery of the gland, thus confirming extrathyroidal extension when they are affected.

Marked Anisocytosis



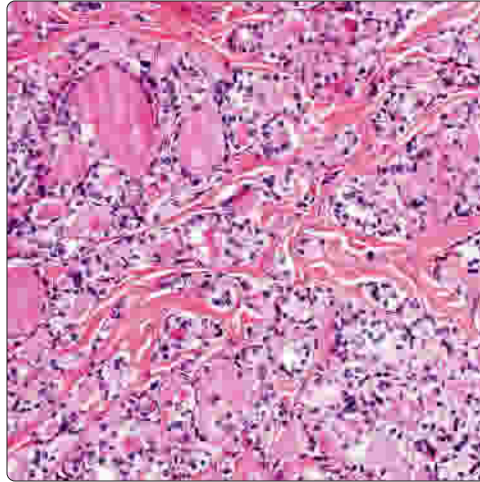
Nuclear Crowding



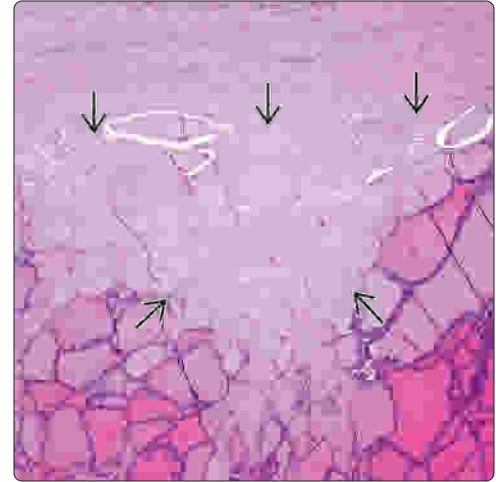
(Left) The background chronic lymphocytic thyroiditis shows oncocytic cells , which are much smaller, lacking the nuclear irregularities and grooves of the PTC cells . (Right) There is nuclear enlargement, irregular placement around the follicles, nuclear overlapping and crowding, and chromatin clearing in this PTC.

Intratumoral Fibrosis

(Left) Intratumor, acellular, sclerotic, dense eosinophilic fibrosis is quite characteristic of papillary carcinoma, seen in up to 90% of cases. There may be irregular, stellate fibrosis extending beyond the tumor in microscopic foci. Sclerotic areas should be sampled at gross exam. **(Right)** Peripheral mummification of the neoplastic cells is a feature found at the tumor to capsule junction. This finding of cell death is not unique to thyroid papillary carcinoma (TPC), but it is infrequently seen in other lesions.

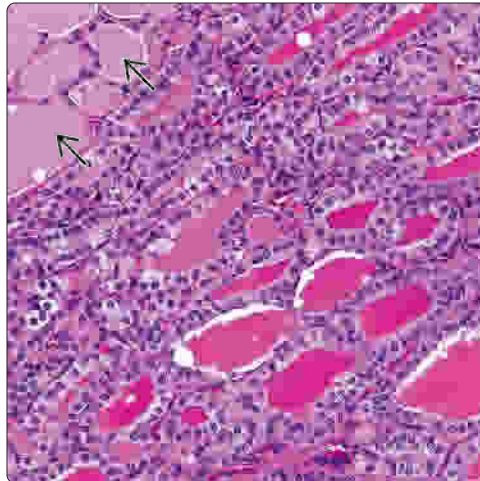


Peripheral Tumor Mummification

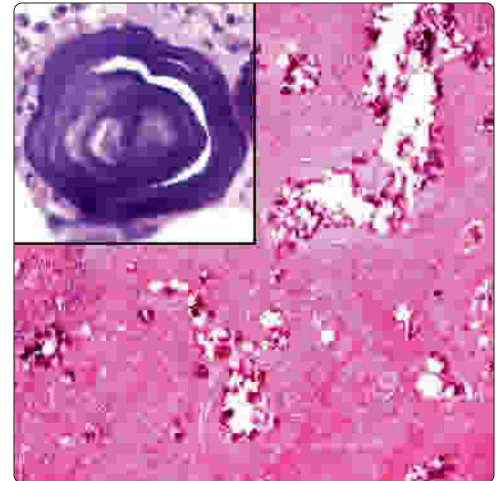


Hypereosinophilic (Bright) Colloid

(Left) This papillary carcinoma highlights the bright, hypereosinophilic, intense colloid within the tumor nests, which is distinct from the adjacent thyroid parenchyma. This was a focus of invasion, lacking a fibrous capsule. **(Right)** Psammoma bodies can be numerous, identified within the tumor, within lymph-vascular spaces, and in lymph nodes. They are a tombstone of previously viable tumor cells. The inset shows a round, concentric lamellation of calcium.

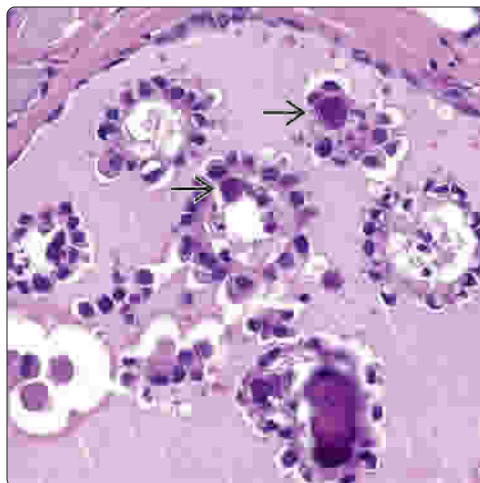


Psammoma Bodies

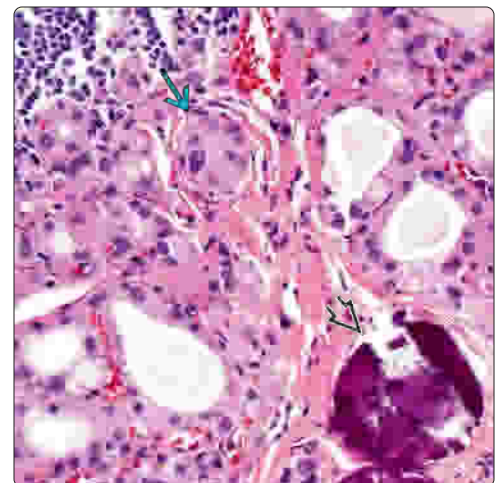


Papillae With Early Psammoma Bodies

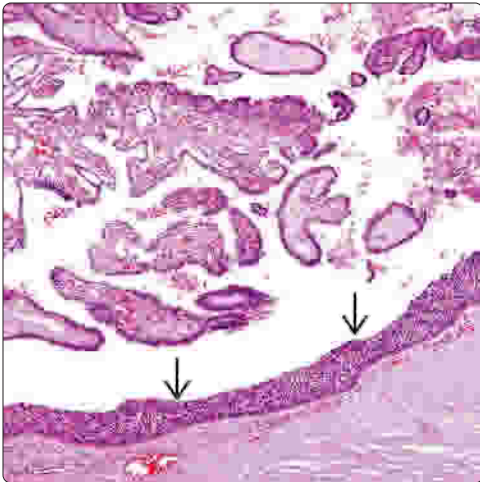
(Left) Psammoma bodies form around a nidus of apoptotic cells that show layers of calcium. Note the start of several psammoma bodies in these papillae. **(Right)** Lymphatic spread of tumor is common, here shown as a viable tumor thrombus and as a psammoma body. The patient had Graves disease.



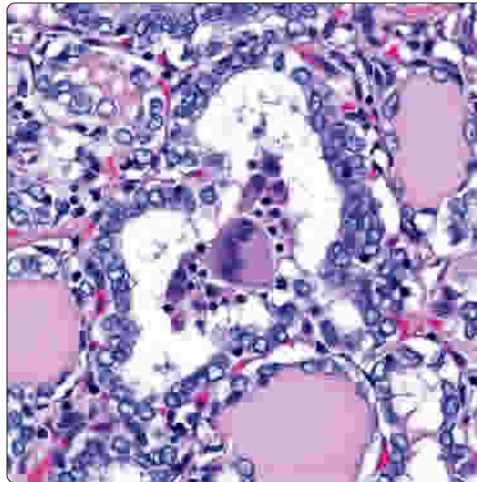
Lymphatic Spread: Viable and Psammoma Body




Squamous Metaplasia in Papillary Thyroid Carcinoma

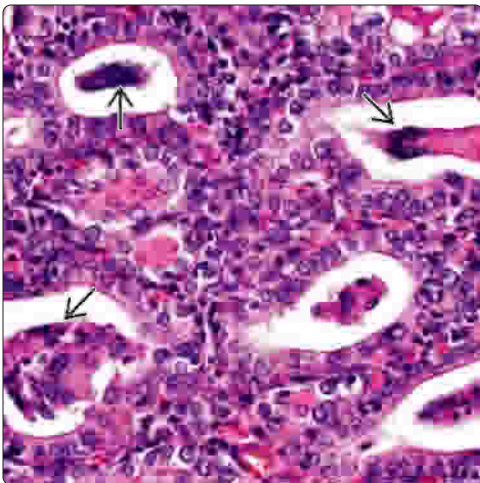


Classical Nuclear Features of Papillary Thyroid Carcinoma

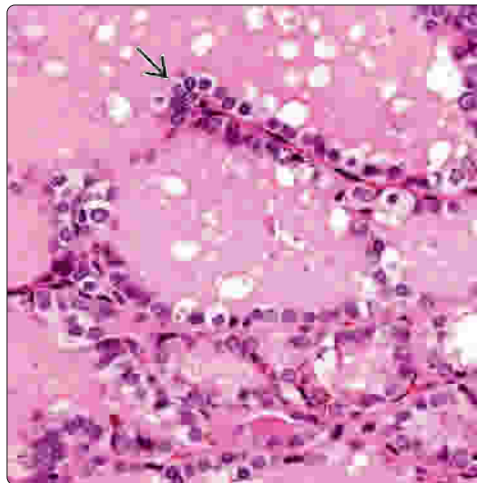




(Left) Squamous metaplasia  is seen in ~ 20% of cases. It may line a cystic cavity (as in this case) or be part of the tumor itself. Squamous metaplasia may be seen in adjacent lymphocytic thyroiditis as well. **(Right)** Classic cytomorphonuclear features are seen: Enlarged cells, high nuclear:cytoplasmic ratio, irregular placement around follicles, nuclear grooves, nuclear contour irregularities, optical clearing, and giant cells within colloid.

Giant Cells in Follicles

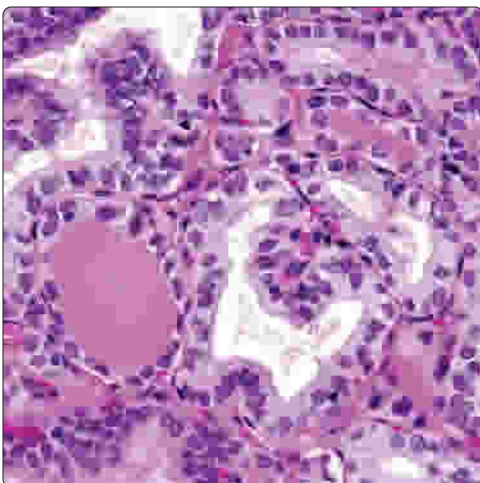


Rigid Papillary Structure

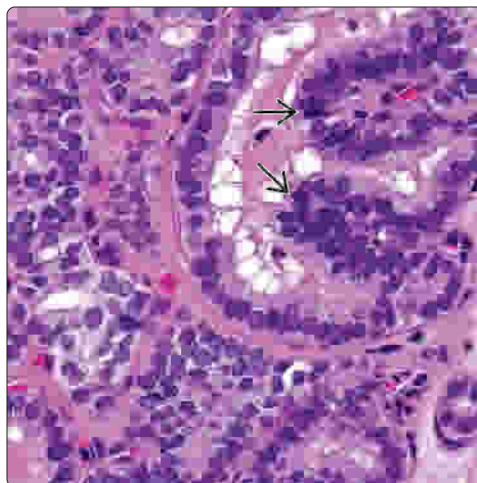



(Left) It is not uncommon to have giant cells  in the follicle or colloid space. They are histiocytes rather than neoplastic giant cells. Although not specific, they can help in diagnostically challenging cases. **(Right)** Delicate, elongated papillae are frequently present . These papillae may extend into a colloid-filled space for quite some distance (up to several hundred μm). This type of rigid papillary projection is more frequent in papillary carcinoma than in adenomatoid nodule.

Pale, Even Chromatin




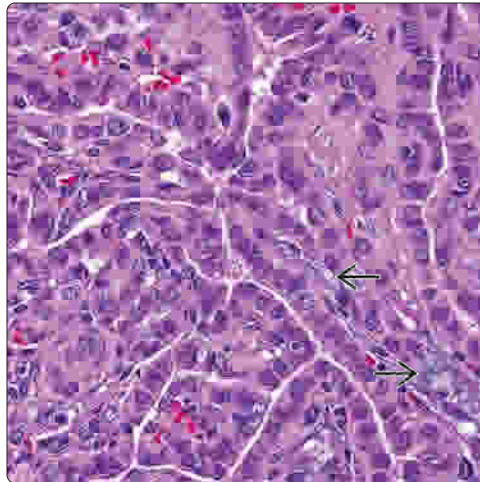
Nuclear Disorganization



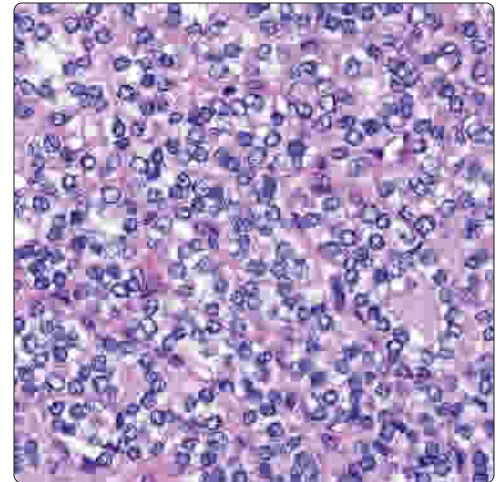
(Left) The nuclei are enlarged, with delicate grooves, showing even, fine nuclear chromatin. This change is not an artifact of processing. **(Right)** The nuclei are frequently overlapped and jumbled or disorganized . This tumor shows areas of overlapping in a lesion that is cut at 4 μm . There is colloid scalloping.

Nuclear Grooves

(Left) The neoplastic cells have a high nuclear:cytoplasmic ratio, showing oval, elongated nuclei with grooves extending along the length of the nucleus. This creates a linear and regular coffee bean appearance. Note the loose myxoid stroma . **(Right)** All of the nuclei in this field show nuclear chromatin clearing, which is sometimes a processing artifact. However, there are grooves, nuclear overlapping, and membrane irregularities that confirm PTC.

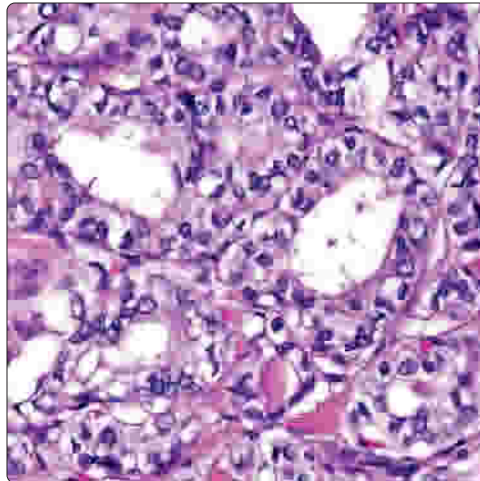


Nuclear Chromatin Clearing

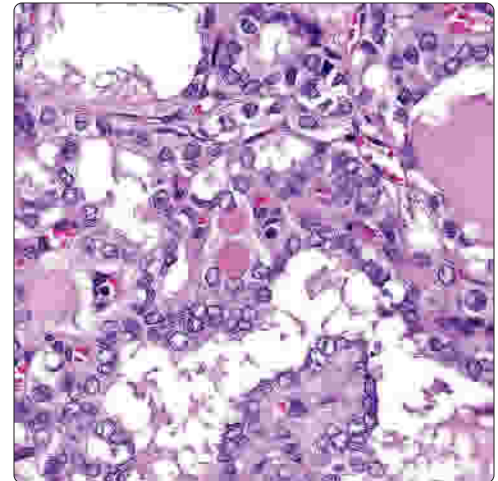


Crescent Moon Shape


(Left) There is nuclear overlapping and crowding, with a lack of nuclear polarity. There are many contour irregularities, creating asymmetric, angulated, crescent moon, convoluted, and triangular shapes. **(Right)** The nuclei are noted at the lumen, middle, and basal zone of the cells, a finding commonly seen in papillary carcinoma.

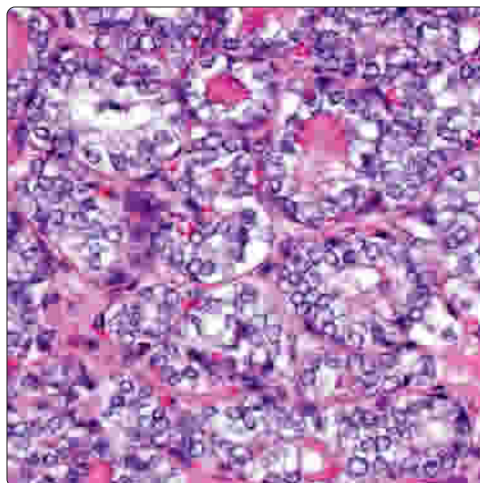


Loss of Polarity

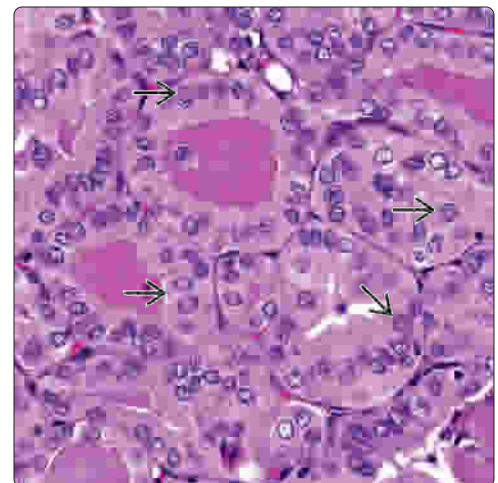


Orphan Annie Eye Nuclei

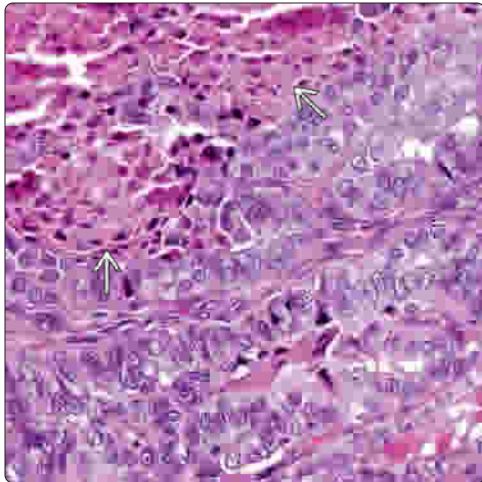
(Left) Nuclear chromatin clearing with accumulation along the nuclear membrane yields accentuated nuclear membranes. The nuclear chromatin is empty, pale, clear, ground-glass, or Orphan Annie eye. Note the crowding. **(Right)** Intranuclear pseudoinclusions are invaginations of the nuclear membrane pulling cytoplasm into the nucleus . They are sharply demarcated with a nuclear membrane, containing material with the same quality as the surrounding cytoplasm.



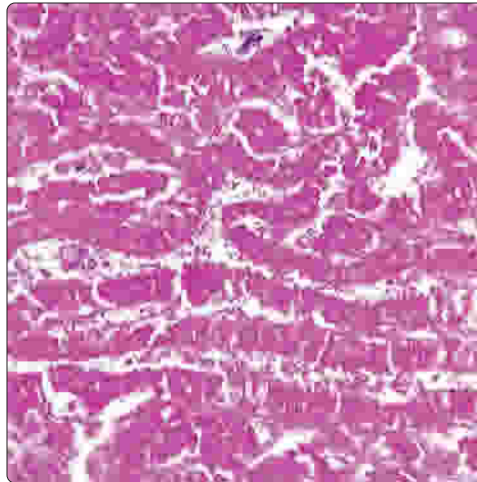
Intranuclear Cytoplasmic Inclusions



Tumor Necrosis

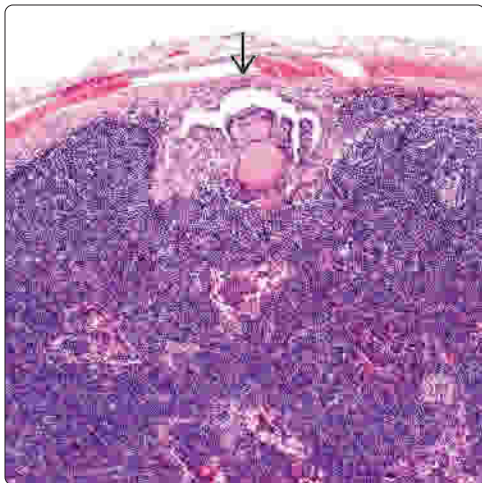


Infarction of Papillary Carcinoma

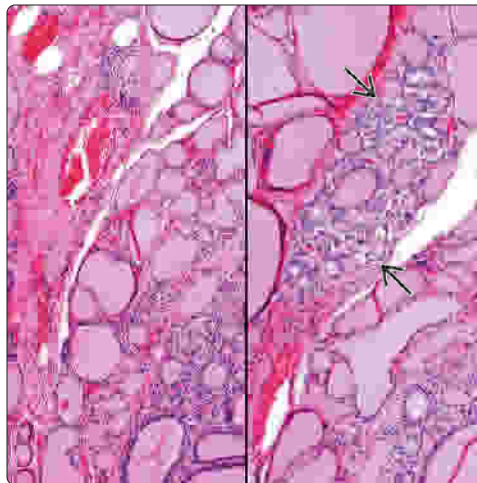


(Left) There is tumor necrosis in this papillary carcinoma. When combined with increased mitoses ($> 4/10$ HPF), the tumor is called poorly differentiated carcinoma. **(Right)** Infarction results in the ghost outlines of the papillary projections. While this is most characteristic of a TPC, viable tumor cells should be identified somewhere to confirm the diagnosis.

Lymph Node Metastasis

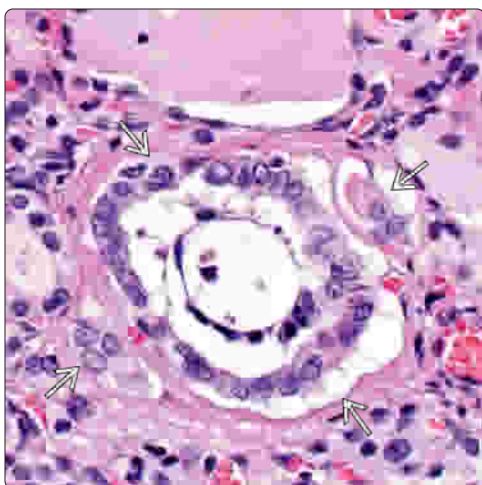


Microscopic Papillary Carcinoma

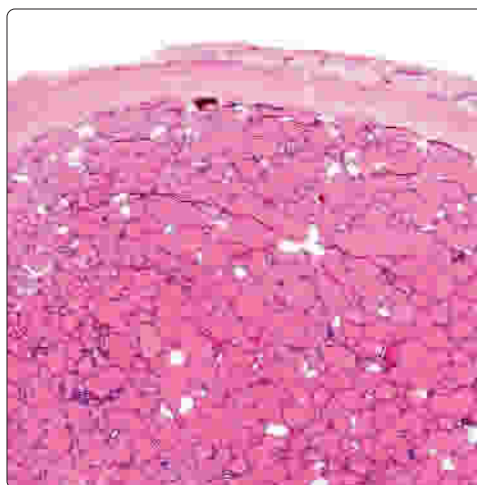


(Left) Metastatic disease is frequently identified. There is a collection of follicular cells within a subcapsular sinus. Psammoma bodies may be the only finding in some cases. Benign inclusions do not exist in cervical lymph nodes of levels II-IV. **(Right)** This tumor was not identified on the original slide (left) but in a deeper level obtained for a different reason, a single focus of microscopic papillary carcinoma is revealed, measuring < 0.1 cm.

Microscopic Papillary Carcinoma



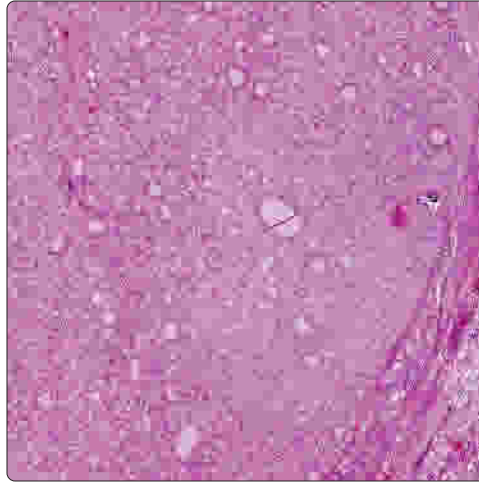
Follicular Variant, Encapsulated Type



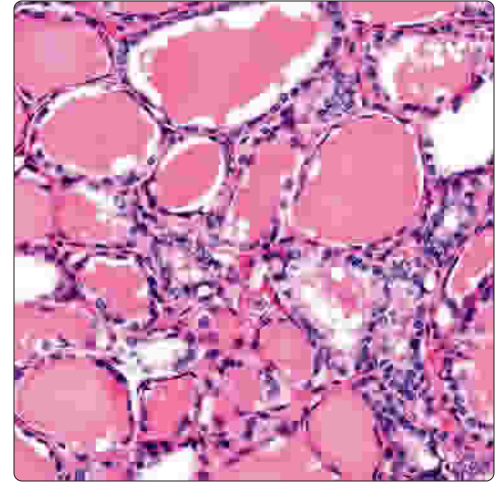
(Left) Only a few follicles, this microscopic papillary carcinoma shows the cytomorphonuclear characteristics of papillary carcinoma. Needless to say, this size tumor is frequently overlooked. **(Right)** There is a very well-formed capsule. Nearly all of the follicles are identical, showing brightly, hypereosinophilic colloid. Papillae are absent. Internal tumor sclerosis or fibrosis is very helpful in diagnosing this variant. Invasion should be documented.

Follicular Variant, Encapsulated Type

(Left) A thin capsule surrounds a tumor composed of fairly uniformly sized follicles without any papillae noted. Invasion must be documented to exclude a noninvasive follicular thyroid neoplasm with papillary-like nuclei. **(Right)** The nuclei lining the follicles show the characteristic features of papillary carcinoma. Many times, a high-power examination of many fields is required to confirm this variant.

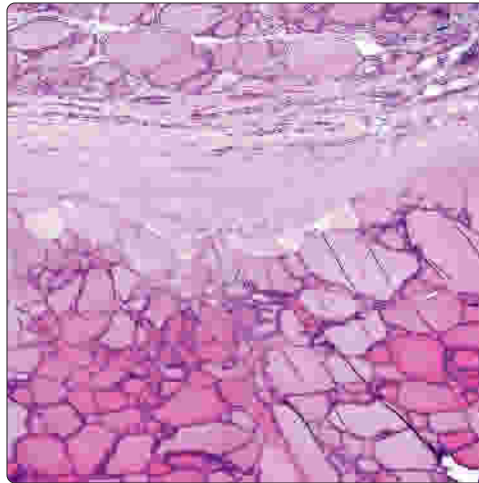


Follicular Variant, Nuclear Features

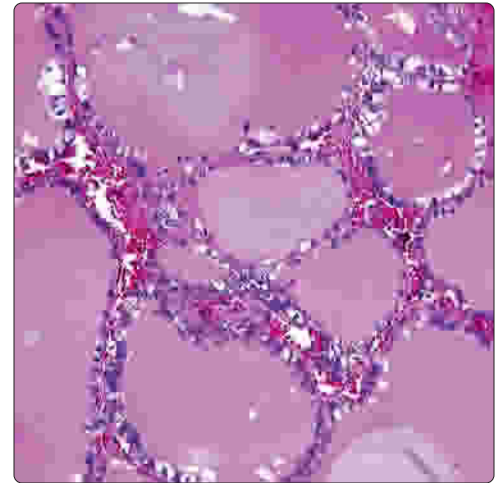


Macrofollicular Variant

(Left) There is a well-formed fibrous connective tissue capsule. The architecture mimics an adenomatoid nodule. There are macrofollicles on low power. A high-power examination is required to confirm the diagnosis in this type of case. **(Right)** The macrofollicles are lined by large cells. Frequently, scalloping or cytoplasmic clearing highlights the atypical neoplastic cells. The nuclei are flattened and hyperchromatic with only isolated classic nuclei.

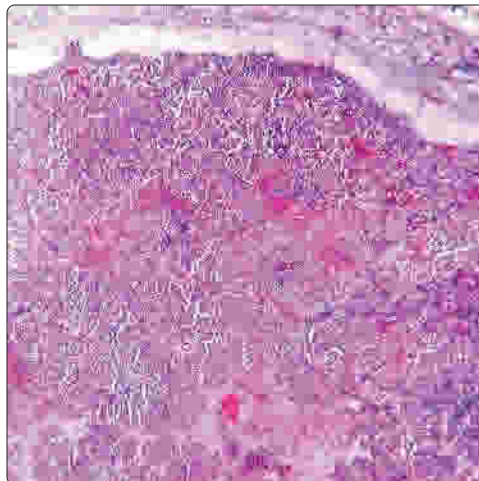


Macrofollicular Variant With Large Follicles

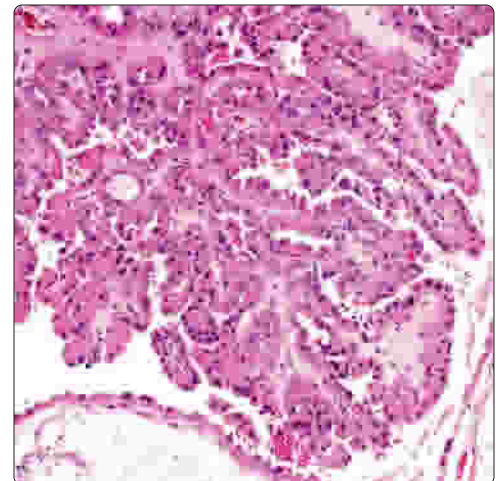


Oncocytic Variant With Papillae

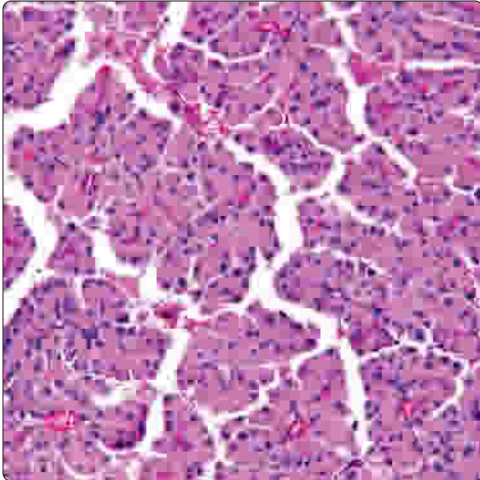
(Left) By low-power examination, at least 70% of the tumor must show a complex, arborizing papillary architecture. Hemorrhage and degeneration are prominent. The cells have abundant oncocytic cytoplasm. **(Right)** There are complex papillary structures showing oncocytic cells with luminal placement of the nuclei. This is a characteristic finding for this variant.



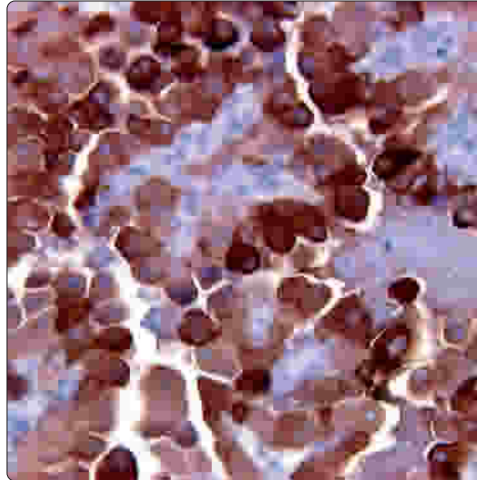
Oncocytic Variant With Complex Papillae



Oncocytic Variant With Luminal Nuclei

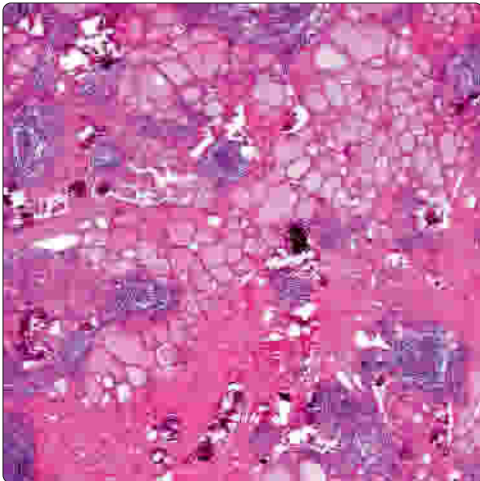


CK19 Reaction in Oncocytic Variant

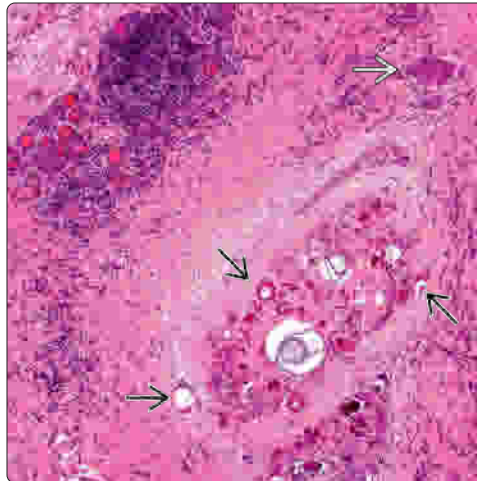


(Left) The cells are enlarged with abundant oncocytic (oxyphilic, Hürthle) cytoplasm. The enlarged nuclei tend to be apically oriented, appearing slightly more hyperchromatic than in conventional PTC. **(Right)** Immunohistochemistry is not usually required for the diagnosis, and when used, should probably incorporate several studies (panel) to confirm the diagnosis. CK19 is frequently positive in oncocytic thyroid papillary carcinoma.

Multiple Foci of Tumor in Diffuse Sclerosing Variant

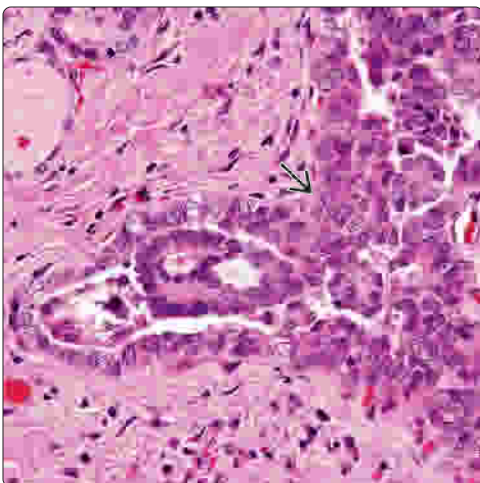


Heavy Sclerosis and Lymphatic Invasion

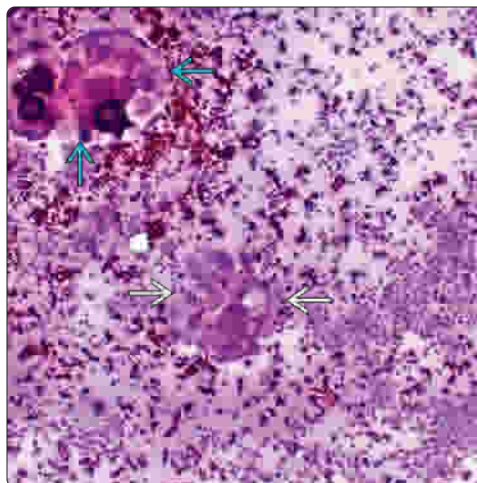


(Left) Diffuse involvement of the thyroid gland by papillary carcinoma is seen with innumerable psammoma bodies, fibrosis, chronic lymphocytic thyroiditis, and extensive lymph-vascular invasion. Diffuse sclerosing variant (DSV) is papillary carcinoma raised to the 3rd power. **(Right)** There is chronic lymphocytic thyroiditis associated with heavy fibrosis. Numerous psammoma bodies [] and areas of squamous metaplasia [] comprise this variant.

Squamous Metaplasia and Fibrosis



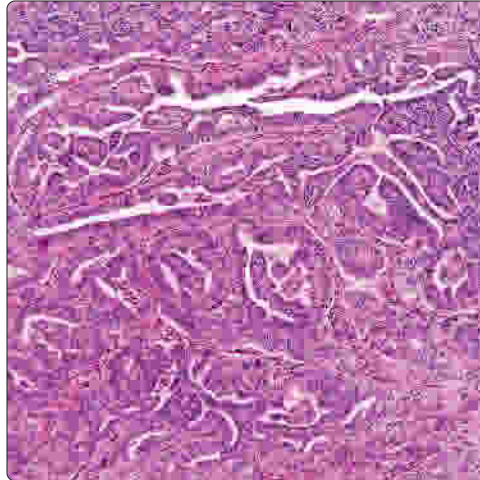
Diffuse Sclerosing Variant on FNA Smear



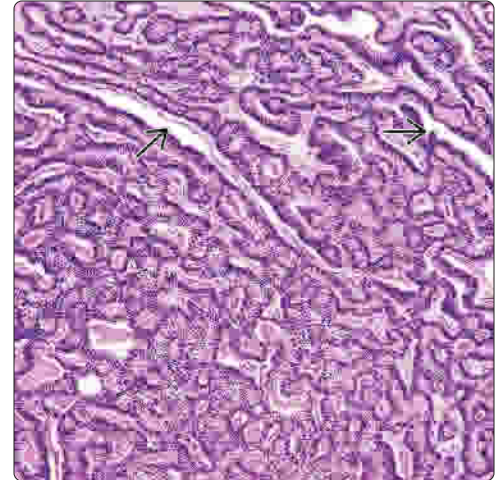
(Left) Papillary carcinoma within a lymph-vascular space, along with areas of squamous metaplasia [], demonstrates background fibrosis. Usually the whole lobe is affected by the neoplastic process. **(Right)** Follicular epithelial sheets are associated with areas of metaplastic squamous epithelium [] along with a cluster of psammoma bodies []. The whole smear appeared this way, suggesting the DSV of PTC.

(Left) There is prominent papillary growth with markedly elongated, parallel follicles. The cells show stratification of the nuclei, creating a look similar to respiratory-type epithelium. **(Right)** The prominent papillary growth shows markedly elongated, parallel follicles (railroad tracks) [2]. There is scant colloid. There is hyperchromasia created by the prominent nuclear stratification of an elongated nuclei with coarse chromatin.

Elongated Follicles in Columnar Variant

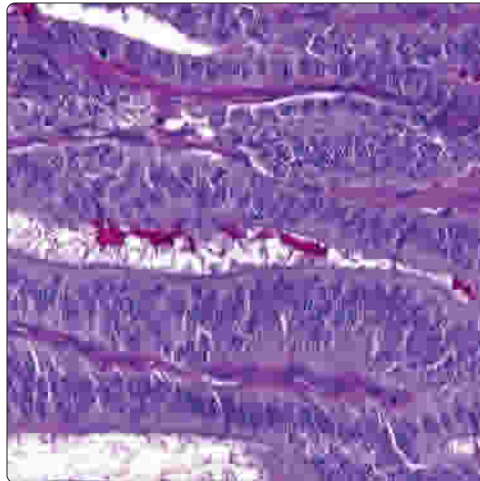


Parallel Elongated Follicles

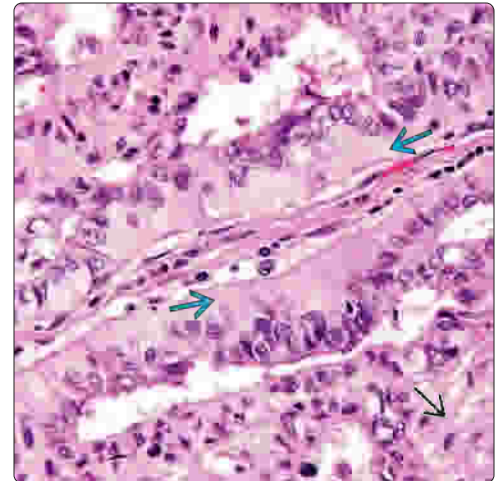


(Left) There is marked nuclear stratification in this columnar variant of papillary carcinoma. The follicles are elongated and there is absent colloid. **(Right)** There are tall cells with a syncytial arrangement showing subnuclear or supranuclear vacuolization [2] of the cytoplasm. An area of necrosis is noted [2].

Nuclear Stratification

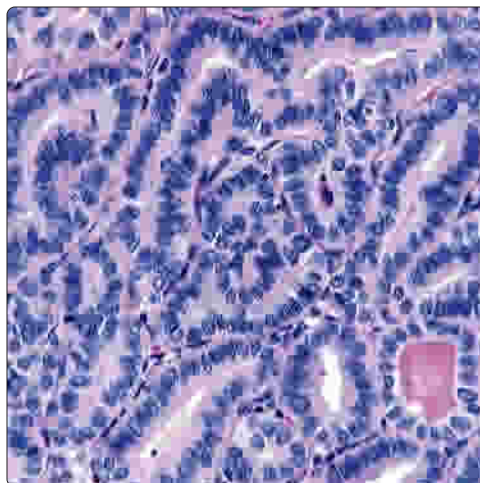


Subnuclear Vacuolization

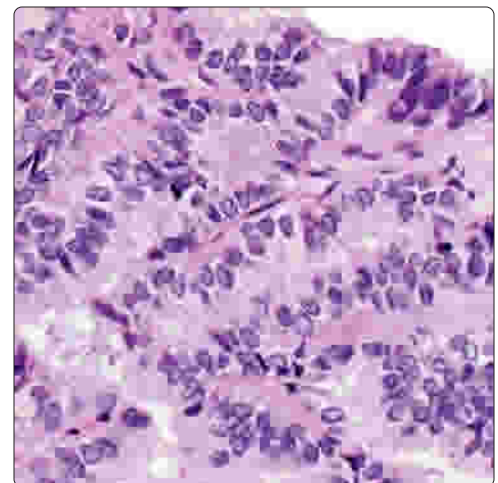


(Left) The cells are tall, measuring at least 3x as high as they are wide (taking plane of section into consideration). Colloid is scant. The intercellular borders are sharply demarcated with centrally located nuclei. Intranuclear cytoplasmic inclusions and nuclear grooves are common. **(Right)** The cells are more than 3x as tall as they are wide, containing nuclei that show the classical nuclear features of papillary carcinoma. This variant has a worse clinical outcome.

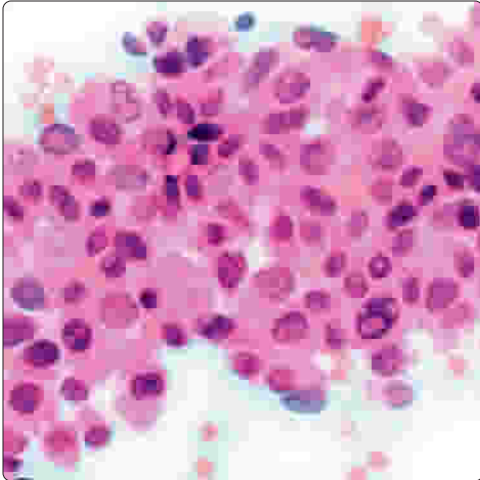
Tall Cell Variant



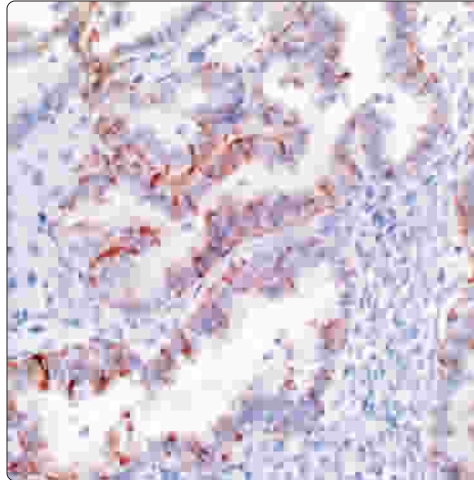
Tall Cell Variant



FNA of Tall Cell Variant



Napsin-A Reactivity in Tall Cell Variant

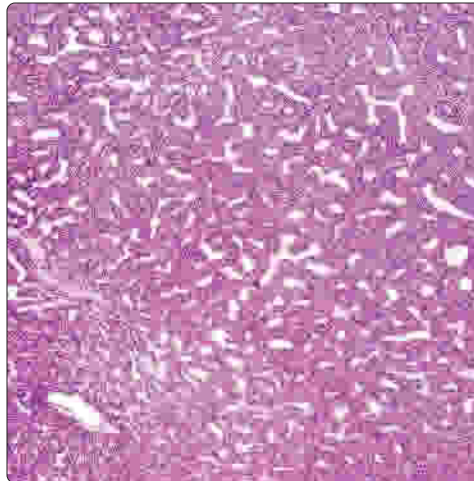


(Left) There is a sheet of highly atypical cells, showing nuclear intranuclear cytoplasmic inclusions. There is architectural disarray and elongated cytoplasm. However, while a variant can be suggested, prospective classification is difficult. **(Right)** Napsin-A is positive in tall cell variants of papillary carcinoma, which may mimic metastatic lung adenocarcinoma, which are also Napsin-A(+) (along with TTF-1). Therefore, thyroglobulin may be needed to help with accurate classification.

Insular Variant of Papillary Thyroid Carcinoma

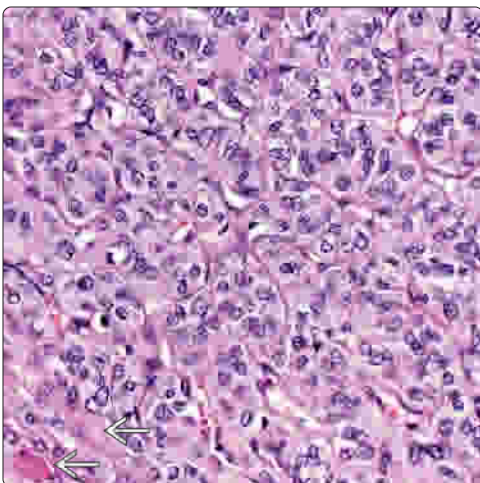


Insular Pattern With Scant Colloid

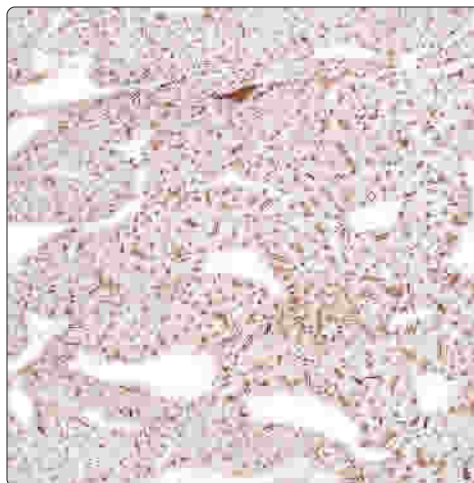


(Left) There is an insular and trabecular architecture to this papillary carcinoma. Nuclear features of papillary carcinoma must be confirmed on high-power examination. **(Right)** A variety of different patterns can be seen in papillary carcinoma. Here, an insular-trabecular pattern predominates, showing scant colloid. The nuclear features are those of papillary carcinoma.

Insular Variant With Papillary Nuclei





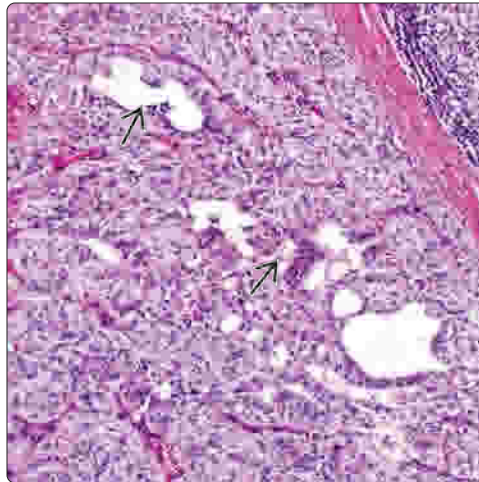
Thyroglobulin Reaction in Insular Variant



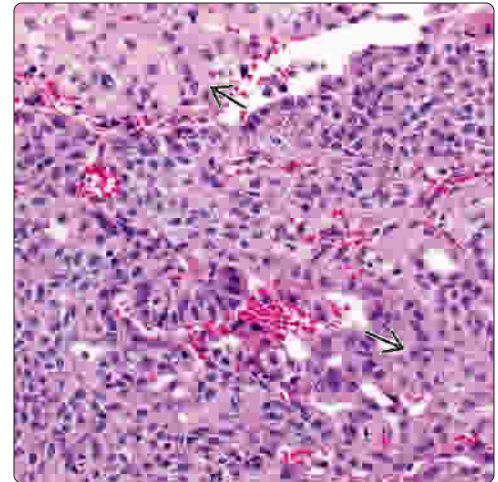
(Left) The classical cytomorphonuclear features of papillary carcinoma are present in this insular variant. There is usually limited colloid in this variant. **(Right)** Due to the limited amount of colloid produced in an insular variant, it is important to confirm thyroglobulin immunoreactivity, thereby excluding other possible tumor types in the differential diagnosis.

Cribriform-Morula Variant


(Left) Usually in a background of chronic lymphocytic thyroiditis, there are small bridges or arches  without colloid in this cribriform-morula variant. **(Right)** There are squamous morules  in the cribriform-morula variant, showing well-developed cell borders. Note the absence of colloid in this variant.

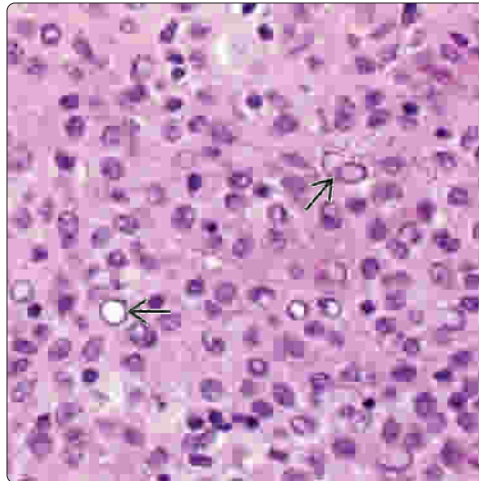


Squamous Morules in Cribriform-Morula Variant

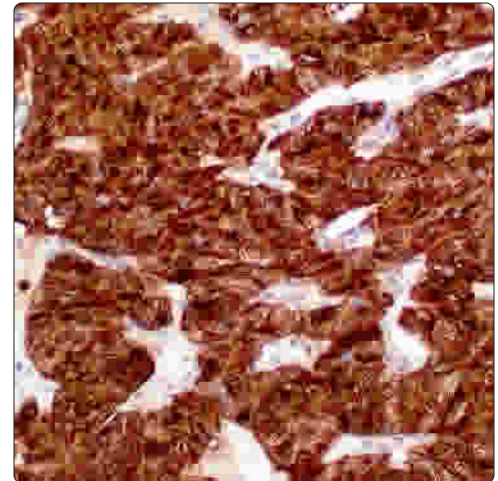


Unique Intranuclear Cytoplasmic Inclusions

(Left) In the squamous morules of the cribriform-morula variant, there are frequent intranuclear cytoplasmic inclusions , which create a nearly complete optical clearing. **(Right)** Due to the strong association with familial adenomatous polyposis (FAP) with APC mutations, which results in Wnt pathway activation, there is a characteristic nuclear accumulation of β -catenin in the cribriform-morula variant, detected by a strong and diffuse nuclear reaction with β -catenin immunohistochemistry.

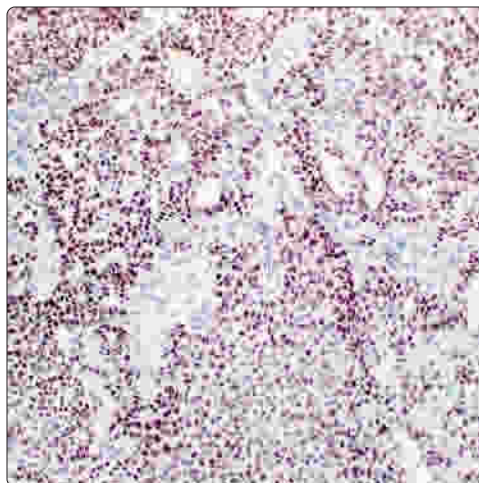


Strong, Diffuse Nuclear β -Catenin Reaction

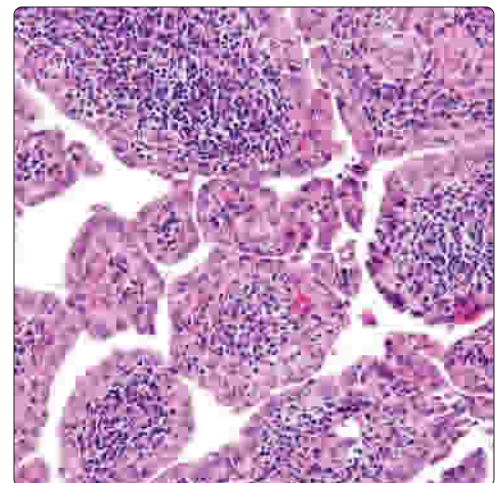


Strong Nuclear Estrogen Receptor Reaction

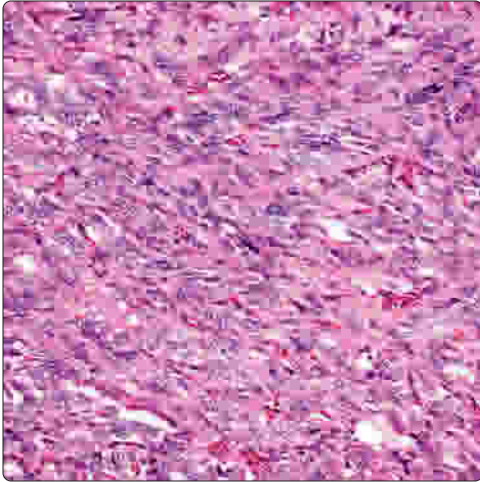
(Left) The cribriform-morula variant shows a characteristic strong and diffuse nuclear reaction with estrogen receptor, a finding not seen in other papillary carcinoma variants. **(Right)** The papillae are expanded and filled with numerous lymphocytes and plasma cells. Lymphoid cells can be seen within the papillae of any papillary carcinoma but are accentuated in this variant.



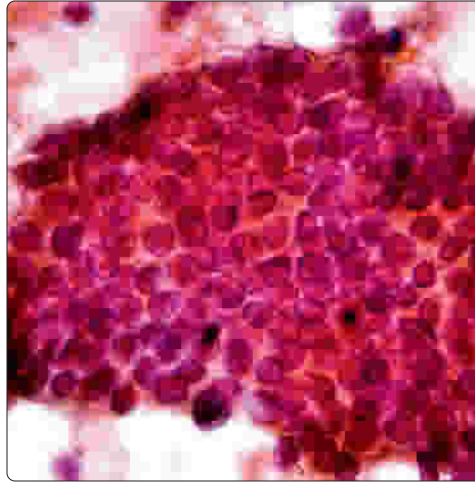
Warthin-Like Variant



Papillary Thyroid Carcinoma With Nodular Fasciitis-Like Stroma

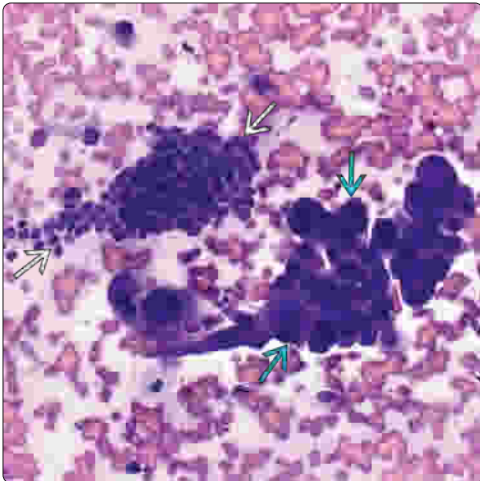


Papillary Carcinoma FNA

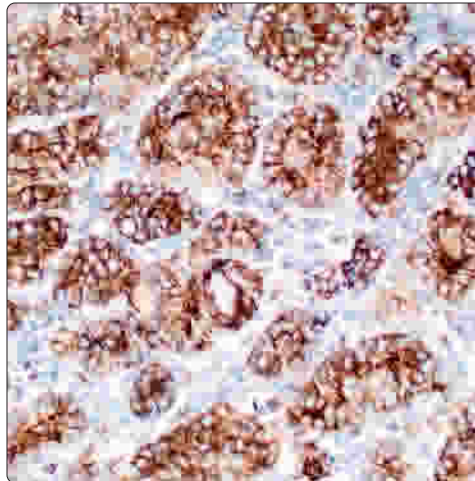


(Left) This is a very uncommon variant of papillary carcinoma that shows a nodular fasciitis-like stroma that is blended with the epithelial papillary carcinoma elements. Post-FNA changes must be excluded. (Right) This fine-needle aspirate (FNA) shows a monolayered sheet with nuclei that are greatly enlarged, overlap, and have irregular borders. There is powdery/dusty, delicate nuclear chromatin, with some nuclear grooves.

Undifferentiated Carcinoma and Papillary Thyroid Carcinoma

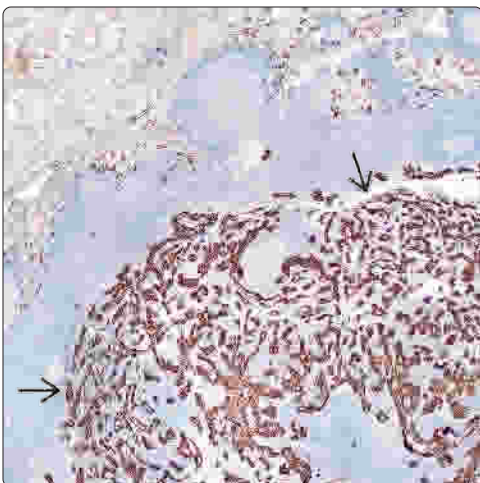


Strong Cytoplasmic Reaction With HBME-1

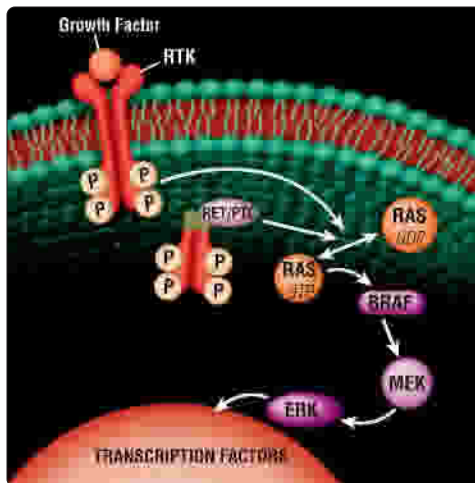


(Left) There is a profound difference between the papillary carcinoma monolayer and the irregular, greatly enlarged cells of the undifferentiated carcinoma. Both tumor types may be concurrently present. (Right) The neoplastic tumor cells are strongly immunoreactive with HBME-1. However, an IHC panel of positive reactions for HBME-1, galectin-3, and MSG1 (CITED-1) may be more sensitive and specific for PTC than HBME-1 alone.

Strong and Diffuse CK19



MAPK1 Pathway in PTC



(Left) Several immunohistochemistry studies are positive in papillary carcinoma, as shown with this CK19 reaction. However, the normal parenchyma is also positive, thus limiting interpretation on an individual basis. (Right) A graphic shows the mitogen-activated protein kinase (MAPK) pathway. Activation of this pathway (point mutation in BRAF and RAS genes or rearrangement involving the RET and NTRK1 genes) is seen in papillary carcinoma.

Follicular Carcinoma

KEY FACTS

CLINICAL ISSUES

- Accounts for ~ 10% of primary thyroid malignancies (0.8/100,000 persons per year)
- 5th and 6th decades; oncogenic: 1 decade older
- Female > male (2-2.5:1)
- Asymptomatic, solitary, painless, slowly enlarging, palpable thyroid mass
- Surgery (lobectomy or thyroidectomy) with radioablative iodine
- 20-year survival: ~ 97% minimally invasive; 50% widely invasive
- Adverse prognostic factors
 - Age > 45 years, extrathyroidal extension, > 4 cm, presence of distant metastases

MACROSCOPIC

- Thicker and more irregular capsule than adenoma
- **Parenchyma-capsule-tumor** zone should be submitted

MICROSCOPIC

- **Either** capsular or vascular invasion is sufficient for diagnosis
- Invasion of vessels within or beyond capsule, showing direct extension, attachment to wall, &/or tumor lined by endothelium
- Microfollicles, solid, cystic, trabecular, insular
- Nuclei are small, round, and regular with smooth contours
- **Variants:** Widely invasive, oncogenic, clear cell

ANCILLARY TESTS

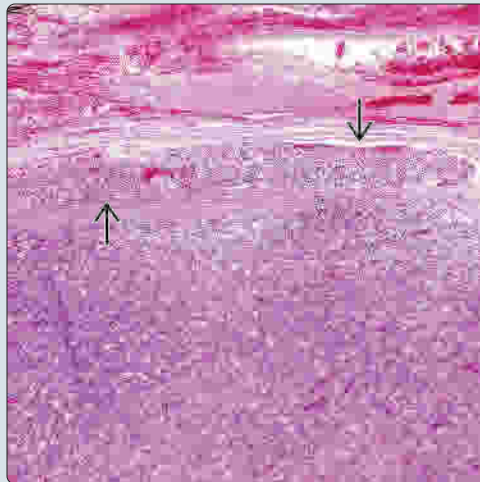
- **Positive:** Thyroglobulin, TTF-1, CK7
- *PPARG* and *RAS* gene rearrangements in 50% of FC

TOP DIFFERENTIAL DIAGNOSES

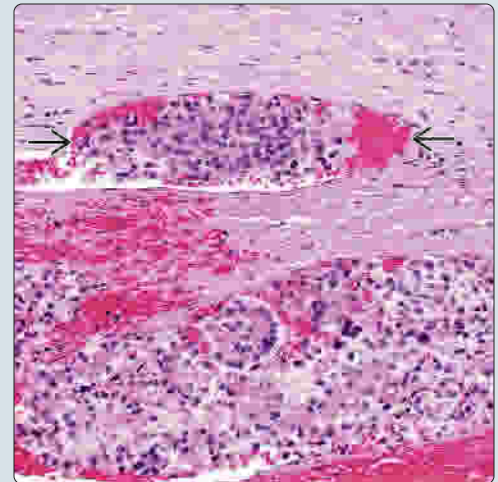
- Follicular adenoma; adenomatoid nodules; noninvasive follicular thyroid neoplasm with papillary-like nuclei
- Papillary carcinoma, medullary carcinoma, and poorly differentiated carcinoma; clear cell neoplasms

Capsular Invasion

(Left) The capsule of this follicular neoplasm shows an island of tumor within the heavy fibrosis [box], confirming a follicular carcinoma. (Right) There is an embolus of tumor [box] noted within a vascular space. An endothelial lining is present, with the neoplastic tumor cells associated with thrombus (erythrocytes and fibrin) within the vascular space.

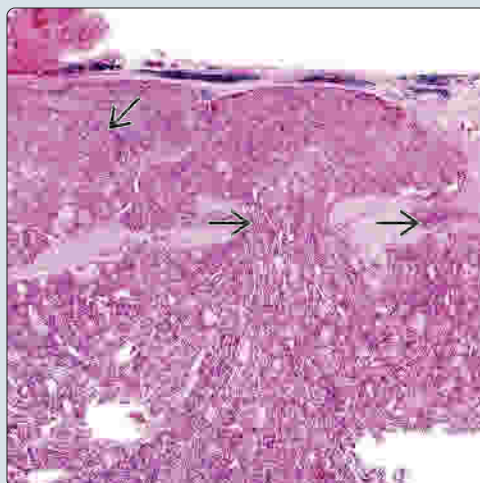


Vascular Invasion



Widely Invasive Follicular Carcinoma

(Left) This widely invasive follicular carcinoma shows numerous areas of capsular invasion [box], creating a mushroom-type pattern. (Right) There is smooth muscle present within the wall of this vascular space, helping to confirm the presence of a true vascular space. There is a large thrombus of tumor [box] within the vessel, attached to the wall.



Tumor Thrombus Within Vascular Space



TERMINOLOGY

Abbreviations

- Follicular carcinoma (FC)

Synonyms

- Follicular adenocarcinoma
- Oncocytic carcinoma
- Hürthle cell carcinoma (discouraged)

Definitions

- Malignant thyroid epithelial neoplasm with follicular cell differentiation and lacking nuclear features of papillary carcinoma
 - Oncocytic (Hürthle cell) follicular carcinoma is most common variant

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Familial syndromes: Up to 4% of FC in USA
 - Cowden disease
 - Autosomal dominant disorder caused by germline mutations in *PTEN* gene located on chromosome 10q22-23
 - Thyroid disease seen in ~ 2/3 of patients, with up to 20% developing FC
 - Werner syndrome
 - Autosomal recessive disease caused by germline mutations in *WRN* gene on chromosome 8p11-12
 - Thyroid disease seen in ~ 3%, usually FC; identified younger than nonaffected patients
 - Carney complex
 - Autosomal dominant disorder caused by germline mutations in *PRKAR1A*

Environmental Exposure

- Iodine deficiency
 - Low dietary iodine intake associated with up to 3x increased risk (compared to areas with sufficient iodine consumption)
 - Low iodine associated with increased TSH stimulation, yielding goiter, promoting follicular carcinogenesis
- Radiation exposure
 - Ionizing radiation exposure results in 5.2x relative risk for developing FC (50% less than papillary carcinoma)
 - Radiation exposure history reported in ~ 4% of FC patients

Preexisting Thyroid Disease

- Identified in up to 15% of patients
- Adenoma
 - Follicular adenoma may be direct precursor lesion (progression to carcinoma)
 - Both harbor *RAS*, *PTEN*, and *PIK3CA* mutations, but carcinoma has higher frequency of mutations
 - Identical histologically except for invasion
 - Carcinomas are seldom small (< 1 cm)
 - Mean age for FC is ~ 8-10 years older than adenoma
- Adenomatoid nodules

- Goiter is associated with increasing rate of cell proliferation due to prolonged TSH stimulation, which enhances chance for mutations in dividing cells
 - Increased occurrence of FC in dys-hormonogenetic goiter patients (inherited defect with highly elevated TSH levels)
- Chronic TSH stimulation needs additional mutagen (radiation or chemicals) to initiate carcinogenesis

Pathogenesis

- Cell of origin is thyroid follicular epithelial cell

CLINICAL ISSUES

Epidemiology

- Incidence
 - All differentiated thyroid cancers represent ~ 1% of human malignancies
 - Annual incidence ~ 0.8 per 100,000 persons per year
 - ~ 10% of primary thyroid malignancies
 - 2nd most common malignancy
 - Trend is downward, as recognition of **follicular variant of papillary carcinoma** has improved
 - Increased in iodine-deficient areas
 - Dietary iodine supplementation associated with decrease in relative frequency of FC
- Age
 - Peak: 50-55 years
 - Oncocytic type: Develops ~ 1 decade later
 - Rare in children
- Sex
 - Female > male (2-2.5:1)
 - Oncocytic type: Female > male (~ 1.7:1)

Site

- Any lobe and in ectopic locations
 - Thyroglossal duct and struma ovarii
- Multifocality is uncommon

Presentation

- Usually present with asymptomatic, solitary, painless, slowly enlarging, palpable thyroid mass
- Tend to be larger than papillary carcinomas
- Nodule usually moves with swallowing
- Lymph node and distant metastasis is uncommon
 - Ipsilateral lymphadenopathy in < 5%
 - Slightly higher in oncocytic variant (lymphatic vs. hematogenous spread)
 - Distant metastases in up to 20% of patients
 - Lungs and bone (bone pain or pathologic fracture)
- Hoarseness, dysphagia, dyspnea, and stridor are rare
- Radiation exposure uncommon

Laboratory Tests

- Thyroid function tests are almost always normal

Treatment

- Options, risks, complications
 - Complications
 - Recurrent laryngeal nerve damage in up to 3%
 - Hypoparathyroidism in up to 3%
 - Hypothyroidism without replacement therapy

- Surgical approaches
 - Surgery (lobectomy vs. thyroidectomy) is treatment of choice
 - Thyroidectomy advocated only to allow subsequent radioiodine therapy and serum thyroglobulin monitoring
 - Hemithyroidectomy: Single nodule, age ≤ 45 years, no thyroiditis
 - Minimally invasive follicular carcinoma
 - **Hemithyroidectomy**: Exclusively capsular invasion, patients < 45 years old, tumor < 40 mm, no metastatic disease
 - **Total thyroidectomy**: ≥ 45 years old, tumor ≥ 40 mm, lymphovascular invasion, metastatic disease
- Radiation
 - Radioablative iodine therapy
 - Cannot be effectively performed **without** total thyroidectomy
 - Up to 30% of tumors fail to take up I-131; therefore, it's ineffective
 - 25% failure for conventional follicular carcinomas and up to 75% failure for oncocyctic carcinoma
 - If there is no lymph node disease, radioactive iodine is not required
 - External beam radiation reserved for incompletely excised tumors, although of questionable value

Prognosis

- Excellent long-term prognosis
 - Minimally invasive: $\sim 97\%$ 20-year survival
 - Widely invasive: $\sim 50\%$ 20-year survival
- Oncocyctic type has same overall outcome as conventional FC
 - Stage-for-stage outcome is similar
 - May be slightly higher incidence of extrathyroidal invasion and local recurrence
 - Associated with increased **lymph node** metastases
- Total thyroidectomy and lobectomy yield **identical** patient outcome
- Adverse prognostic factors
 - Age > 45 years
 - Extrathyroidal extension
 - Tumor size > 4 cm
 - Presence of distant metastases
- If metastatic, lung and bones are most common
 - Lymph nodes: Oncocyctic type (10% of cases)
 - Rarely: Kidney, soft tissue, adrenal, and eye
- RAS mutations correlated with tumor dedifferentiation, distant metastases, shorter survival
- Indeterminate (atypical) follicular neoplasm cases usually have benign outcome

IMAGING

Radiographic Findings

- Imaging cannot reliably distinguish between benign and malignant thyroid lesions
- MR is preferred over CT: Iodinated contrast to be avoided, as it delays I-131 therapy
- Nuclear scintigraphy
 - Usually "cold" on scintigraphic scan

- May be used to detect recurrence/metastasis post thyroidectomy
- FC tend to concentrate I-131 less than adjacent normal thyroid parenchyma

Ultrasonographic Findings

- Used to follow nodules serially over time and for FNA guidance
- Ultrasound usually shows solid, hypoechoic mass with peripheral nonechogenic halo (capsule)
- Irregular and poorly defined margins and turbulent intratumor blood flow suggest carcinoma

MACROSCOPIC

General Features

- Encapsulated round to ovoid, solitary, solid tumors
- Thicker and more irregular capsule than adenoma
- Cross section has bulging, fleshy surface
- Widely invasive FC may show capsular and vascular invasion (including vena cava)
 - Sometimes encapsulation is difficult to document
- Hemorrhage, necrosis, and infarction are uncommon
- Gray-white to brown-tan or mahogany-brown (oncocyctic carcinoma)

Sections to Be Submitted

- Serial sections of nodule at 2-3-mm intervals
- Unless large, entire **parenchyma-capsule-tumor** zone should be submitted
 - Minimum of 10 blocks (2-3 sections per block) from capsule-tumor interface

Size

- Most are 2-4 cm
 - Oncocyctic tumors may be larger

MICROSCOPIC

Histologic Features

- Majority are conventional type ($\sim 20\%$ are variants)
- Lack nuclear features of papillary carcinoma
- Tumor surrounded by capsule
 - Deposition of parallel layers of collagen fibers surrounding tumor and containing smooth muscle-walled vessels
 - Reticulin fibers within connective tissue
 - Thick and well formed (0.1-0.4 cm thick)
 - Should completely encapsulate lesion
 - Thin, irregular, attenuated, uneven, and poorly formed (< 0.1 cm thick) may be seen
- **Either** capsular or lymphovascular invasion is sufficient for diagnosis
- **Invasion** must be present
 - **Capsular invasion**
 - Penetration of $> 1/2$ thickness of capsule (partial thickness)
 - Beyond contour of tumor nodule
 - Unassociated with site of previous FNA
 - Direct contact of tumor cells with thyroid parenchyma is rare because new collagen is deposited around advancing edge

- Deeper sections may show tumor connection of "satellite" nodule adjacent to parenchyma
- Tangential sectioning frequently limits interpretation
- **FNA artifact:** Abrupt capsular loss, linear tract, reactive endothelial proliferation, hemosiderin, erythrocytes, foreign body giant cells
- **Vascular invasion**
 - Vessels are within or beyond capsule, **not** within tumor
 - Direct tumor extension into vessel
 - Tumor cells must be identical to those within main tumor
 - Vascular space needs to be lined by endothelial cells
 - Tumor **attached** to vascular spaces
 - Associated thrombus/fibrin helps to confirm that tumor has incited response by entering vessel lumen
 - **Not** entrapped cells with retraction artifacts
 - **Not** free-floating, nonviable cells in serum
 - **Not** result of surgical or sectioning manipulation
 - Be aware of "penetrating" vessels: Tangentially sectioned vessels
- Exact number of vessels involved or areas of capsular invasion not defined
 - However, > 4 vessels affected are used as cut-off for separation between minimally invasive and invasive tumors
- Tumor cells arranged in well-formed follicles (microfollicular), solid, cystic, trabecular, and insular patterns
 - 1 pattern usually predominates
 - Macrofollicular patterns are uncommon
- Tumors are cellular, but colloid is usually easily identified
 - Oncocytic tumors may show more limited colloid
 - Colloid can be confirmed with thyroglobulin &/or PAS stains
- Tumor cells are slightly larger than adjacent parenchyma, cuboidal, and regular
 - Focal tumor cell spindling can be seen
 - Cytoplasm is ample, lightly eosinophilic to amphophilic
- Nuclei are small to medium, usually round and regular with smooth contours
 - Nuclear chromatin is coarse and heavy
 - Nucleoli are small
 - Isolated nuclear pleomorphism can be seen but does not alter diagnosis
- Mitotic figures may be seen but are usually $\leq 3/10$ HPF
- Degeneration and necrosis are uncommon
 - May be present in post-FNA tumors
- Direct soft tissue and tracheal extension is rare
- Intrathyroidal spread is not seen

Margins

- Surgical margins should be reported
- Extension beyond thyroid gland into adjacent soft tissues is associated with more biologically aggressive behavior

Variants

- **Widely invasive**
 - Uncommon, as result of improved physician and patient awareness, superior radiographic techniques, and advances in surgical management

- Usually in older patients, patients with larger tumors, and patients with higher postoperative thyroglobulin levels
- Extensive capsular invasion ("mushroom" invasion)
 - Capsule may be lost or hard to identify
- Direct extension into adjacent thyroid parenchyma or perithyroidal soft tissue
- Extensive vascular invasion: Large vessels (arteries, veins, lymphatics) and perithyroidal vessels

● Oncocytic variant

- a.k.a. Hürthle cell, Ashkenazy cell, oxyphilic cell: Due to increased accumulation of abnormal mitochondria
 - These terms are discouraged
 - Ashkenazy described cells first in 1898
 - Hürthle described C cells in dogs
- Tumors tend to be larger than conventional FC
- Macroscopically, mahogany brown appearance is distinctive
- Invasive criteria identical to conventional FC
- > 75% of tumor composed of oncocytic cells
 - Large, polygonal cells with well-defined cell borders
 - Abundant, fine to slightly coarse, granular, deeply eosinophilic cytoplasm
 - Opacified or smooth cytoplasm
 - Nuclei: Round and regular with coarse chromatin
 - Frequently associated with prominent, brightly eosinophilic, centrally placed nucleoli
 - Pleomorphism is increased in this variant
- Cytoplasm is more fragile, with tendency to undergo infarction, usually post FNA
 - Hemorrhage, degeneration, and eventual fibrosis may result
- Solid and trabecular patterns show scant/absent colloid
 - TTF-1 or thyroglobulin useful in these cases
- Colloid tends to be basophilic and undergo calcification (mimic of psammoma bodies)

● Clear cell variant

- Predominantly (> 75%) composed of clear cells
- Cytoplasm is watery clear or has fine, pale eosinophilic granularity
- Quality of cytoplasm due to accumulation of glycogen, lipid, thyroglobulin, other vesicles, or distended mitochondria
 - May be seen in oncocytic tumors especially
- Should be separated from metastatic renal cell carcinoma and clear cell medullary carcinoma (by immunohistochemistry)

● Signet-ring variant

- Cells with large intracytoplasmic vacuoles that displace and compress nucleus to side
 - Material is immunoreactive for thyroglobulin and positive with PAS-diacetate
- Invasion must be identified

● Mucinous variant

- Exceedingly rare, with pools of stromal and intraluminal mucin (mucicarmine positive)

ANCILLARY TESTS

Cytology

- Separation of adenoma/nodule from carcinoma **cannot** be reliably or predictably performed by FNA

- Sensitivity: 78%
- Specificity: 98%
- Positive predictive value: 99%
- Hypercellular aspirates
- Dispersed microfollicles
 - Groups of follicular cells with 6-12 nuclei forming ring-like structure
 - Spherical, 3D aggregates
 - Enlarged cuboidal cells with uniform, round, smooth nuclei with coarse nuclear chromatin
 - Cytoplasmic borders are frequently indistinct
 - Nuclear size and shape variability
- Scant colloid
- **Oncocytic variant:** Scant colloid; dyscohesive cells; large round to oval cells; low nuclear:cytoplasmic ratio; abundant granular cytoplasm; eccentric round nuclei; bi- or multinucleation may be seen; nucleoli usually prominent; no lymphoplasmacytic infiltrate
- ~ 20-30% of Bethesda Follicular neoplasms (IV) and follicular lesion of undetermined significance (III) collectively are malignant on final pathology
- Molecular testing: May reduce number of unnecessary thyroid procedures; may reduce number of completion thyroidectomies; may yield more individualized operative and postoperative management
 - Targeted testing for *BRAF*, *RAS*, *RET/PTCH1*, *TERT*, and *PAX8/PPARG* improve specificity of FNA
- Thyroglobulin measurement in needle washout after FNA of lymph nodes shows good sensitivity/specificity with metastatic disease

Frozen Sections

- Nearly completely useless unless you happen upon area of invasion
- If FNA has been performed, decline frozen
- If frozen is demanded, 2-3 sections of capsule sampled, before "**defer to permanent**" is used

Histochemistry

- PAS highlights colloid

Immunohistochemistry

- **Positive:** Thyroglobulin, TTF-1, CK7
 - **Panel** positive with galectin-3, HBME-1, MSG1; may be helpful to confirm malignancy
 - Caution: Oncocytic tumors show nonspecific staining and high endogenous biotin activity
- **Negative:** Chromogranin, calcitonin, synaptophysin, CD56, CEA-M
- CD34, CD31, FVIII-RAG can accentuate vessels (very limited value)

Flow Cytometry

- Aneuploidy in 50-60% of FC

Genetic Testing

- *PAX8/PPARG* rearrangements found in up to 50% of FC
 - t(2;3)(q13;p25) leads to fusion between *PAX8* gene on 2q13 and *PPARG* gene on 3p25
 - FISH generally used for detection
 - Patients tend to be younger; tumors are smaller; solid growth pattern
 - Almost never show concurrent *RAS* mutations

- *RAS* abnormal in up to 50% of FC (not carcinoma specific)
 - Activating mutations in codon 61 of *N-RAS* and *H-RAS* genes are most common
 - Follicular adenoma and follicular variant of papillary carcinoma also show *RAS* mutations
- *GRIM-19* gene mutations identified in oncocytic tumors
- High rate of loss of heterozygosity is characteristic of FC
 - Known tumor suppressor genes: *VHL* on 3p25-26, *TP53* on 17p13, *PTEN* on 10q23
- Mutations lead to activation of MAPK and *PIK3CA-AKT1* signaling pathways, considered crucial in carcinogenesis

Electron Microscopy

- Follicular cells with preserved polarity; cells resting on continuous basal lamina; microvilli on apical surface; nuclei with finely dispersed chromatin, well-developed granular endoplasmic reticulum
- Oncocytic cells filled with abnormal mitochondria showing variability in size and pleomorphism, showing disappearance of cristae

DIFFERENTIAL DIAGNOSIS

Follicular Adenoma

- Encapsulated, single tumor without invasion
- Histological features identical to carcinoma
- Periphery must be adequately sampled

Adenomatoid Nodules

- Usually multiple lesions
- Usually less cellular with more colloid than neoplasms
- Tend to have irregular fibrosis rather than capsule
- Lack muscle-walled vessels in fibrous connective tissue
- Tangential sectioning, irregular contours, FNA, and frozen section artifacts hamper interpretation

Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclei

- Partially to completely encapsulated tumor
- No evidence of either capsular or lymphovascular invasion
- 99% of tumor arranged in follicular architecture; <1% of tumor volume may have papillae
- Absence of insular, trabecular, or solid growth
- Absence of tumor necrosis or increased mitoses (≤ 3 mitoses/10 HPF)
- Hypereosinophilic colloid within follicles
- Internal sclerotic fibrosis (intratumoral fibrosis)
- Characteristic nuclear features of papillary carcinoma
 - Nuclear enlargement, nuclear crowding or overlapping, contour irregularities, nuclear grooves and folds, nuclear chromatin clearing, prominent nuclear membranes
- Most show *RAS* mutation

Papillary Carcinoma

- Specifically, follicular variant
- May or may not show encapsulation, but invasion (capsular or lymphovascular) is present
- Follicular architecture predominates, with intratumoral fibrosis and hypereosinophilic colloid
- Characteristic nuclear features of papillary carcinoma

Somatic Mutations in Thyroid Follicular Carcinoma

Mutation Type	Follicular Carcinoma	Oncocytic-Type Follicular Carcinoma
<i>RAS</i> point mutations	40–50%	10–15%
<i>PAX8/PPARG</i> rearrangement	30–40%	0–5%
<i>PTEN</i> point mutations, small deletions	5–10%	NR
<i>PIK3CA</i> point mutations	5–10%	NR
NR = not yet reported.		

- o Nuclear chromatin clearing, contour irregularities, nuclear grooves, nuclear overlapping, intranuclear cytoplasmic inclusions
- Most show *RAS* mutation

Medullary Carcinoma

- Cellular tumors, lacking colloid
- Amyloid is often present
- Background of C-cell hyperplasia in inherited tumors
- Nesting or insular architecture
- Oval to spindle cells
- Round, eccentric nuclei with finely stippled chromatin
- Positive with chromogranin, synaptophysin, calcitonin, CEA-M, CD56

Poorly Differentiated Carcinoma

- Solid, trabecular, and insular growth patterns require separation from poorly differentiated carcinomas
- Increased mitotic figures (≥ 4 mitoses/10 HPF) and necrosis move follicular-derived tumors to poorly differentiated category
- Often have relative lack of colloid production

Clear Cell Neoplasms

- Parathyroid neoplasms
 - o Adenoma or carcinoma show parathyroid hormone and chromogranin reactivity
- Metastatic renal cell carcinoma
 - o Immunohistochemical studies can help
 - o Do not overinterpret entrapped thyroid follicular cells as tumor cells positive with TTF-1 or thyroglobulin

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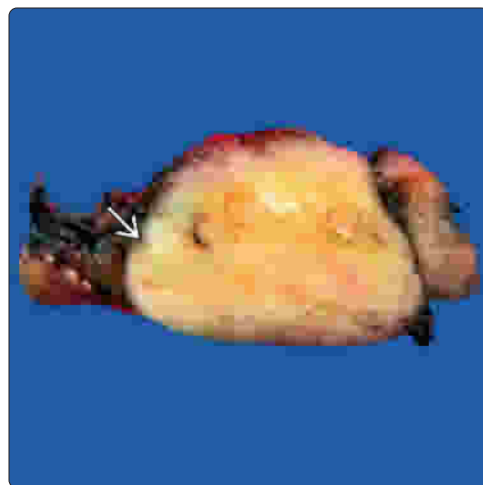
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CT of Thyroid Gland Tumor

(Left) CT shows a large, solid, well-circumscribed thyroid neoplasm lacking capsular invasion. This is a common but nonspecific finding in radiographic imaging of thyroid lesions, which may be seen with benign or malignant lesions. (Right) There is a solid tumor in the thyroid gland. The cut surface appears quite light in comparison to the surrounding parenchyma. An area of extension is suggested, although, not diagnostic of capsular invasion.

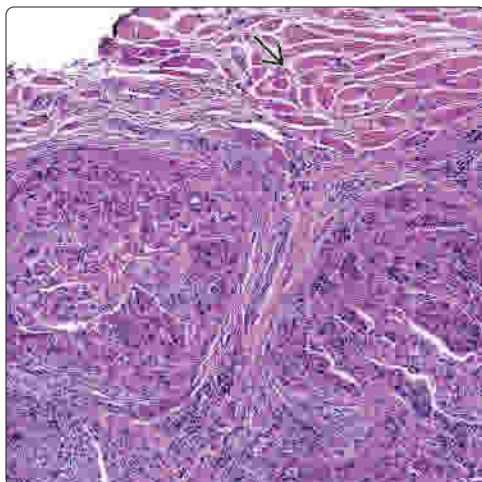


Solid Tumor Within Thyroid Gland

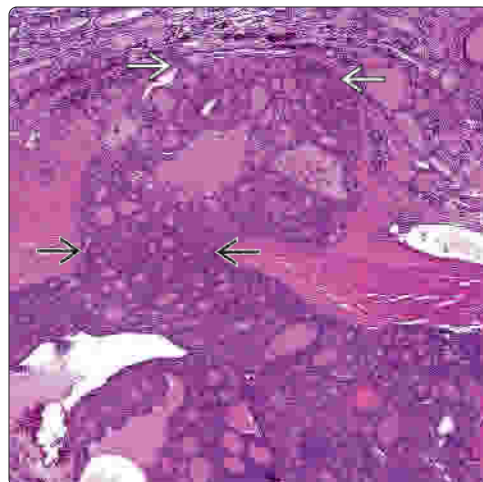


Extrathyroidal Extension

(Left) Thyroid carcinomas may demonstrate extension beyond the thyroid gland parenchyma into the adjacent soft tissue. Here, the tumor is identified blending with the skeletal muscle. Normal isthmus follicular epithelium may also be blended with skeletal muscle. (Right) Full penetration of the capsule is diagnostic of follicular carcinoma. However, sometimes the invasion is not as well developed, as seen here. Note the new collagen deposition at the leading edge of the tumor nodule.

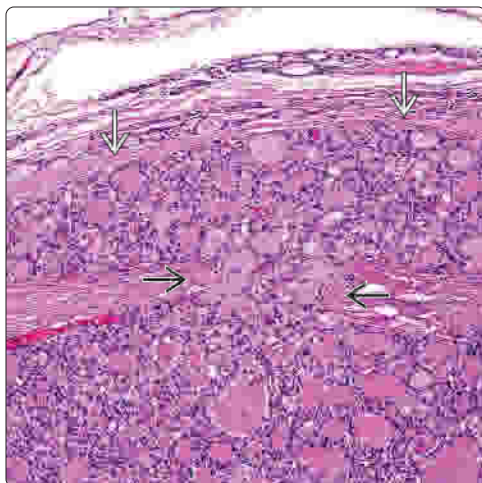


Capsular Invasion

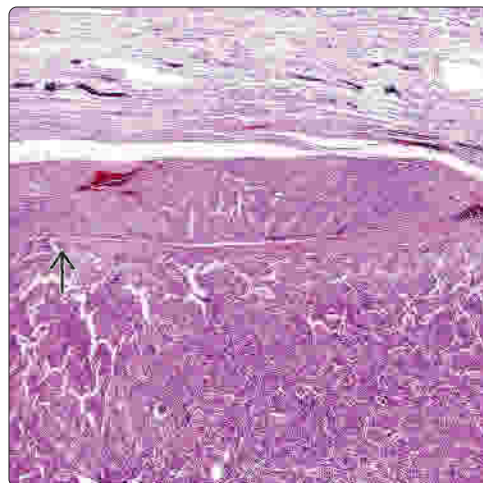


Capsular Invasion

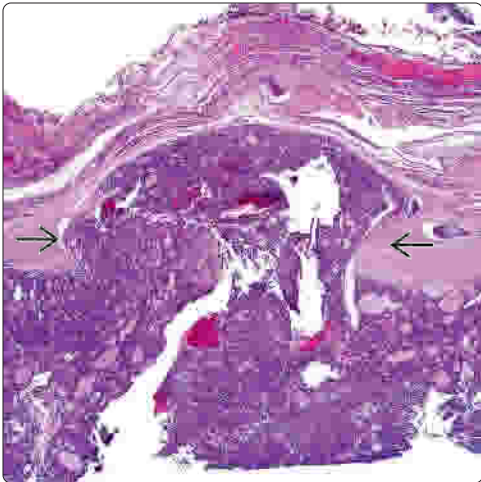
(Left) The tumor capsule is breached by the neoplastic cells, which have formed a "mushroom" as it expands into the surrounding parenchyma. Note the new collagen deposition at the leading edge of the tumor projection. (Right) This well-formed capsule demonstrates an area of capsular invasion. The neoplastic cells are noted parallel to the capsule, demonstrating invasion through the capsule, and then alignment parallel to the fibrosis.



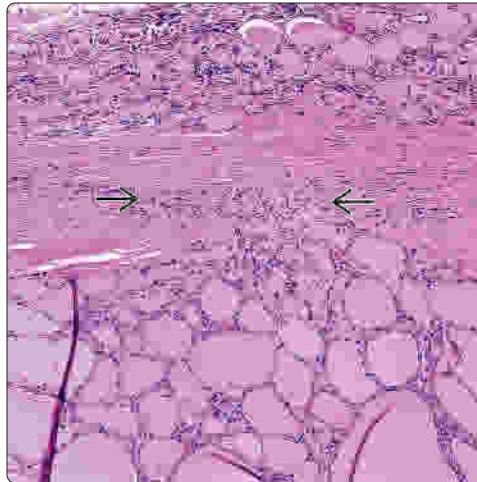
Capsular Invasion



Mushroom of Tumor Through Capsule

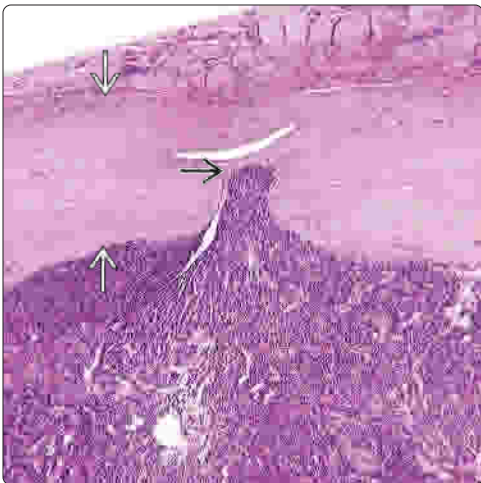


Partial Capsular Penetration

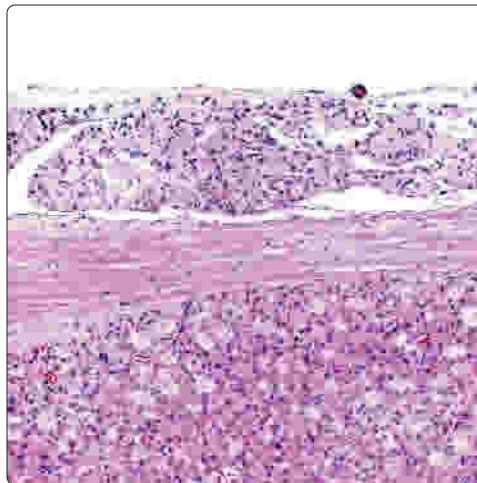


(Left) In some tumors, the capsular penetration may "push" the capsule up to the point where the tumor projects well beyond the contour of the tumor [X]. It is important to review the capsule at low power to get a sense of the tumor shape and periphery. (Right) This focus [X] is insufficient to qualify as true capsule invasion, although, the capsule is partially penetrated by the neoplastic cells. In cases like this, additional levels or sections are suggested to exclude invasion.

< 50% Capsular Penetration

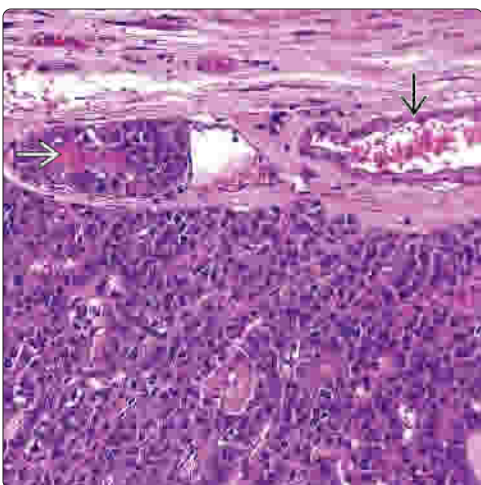


Lymphatic Invasion



(Left) This was the only focus of capsular permeation [X] in a thoroughly sampled tumor. The capsule is very thick [X], and the tumor is cellular. However, this area does not quite reach the threshold for capsular invasion. (Right) There is a delicate endothelial lining of the lymphatic space in the tumor capsule. This area is diagnostic of invasion and would qualify as lymphatic invasion.

Vascular Invasion





Large Vessel Invasion

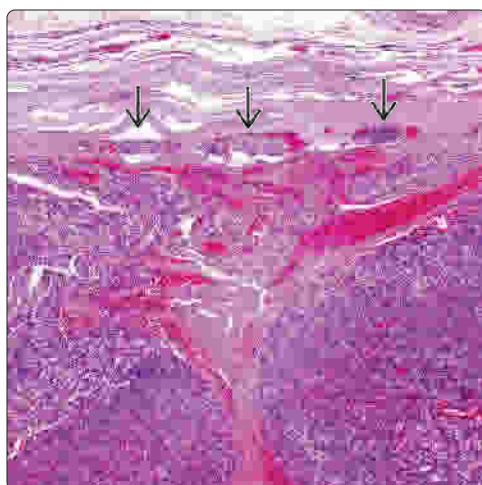


(Left) The vessel is filled with tumor, including an area of colloid production [X]. The wall of the vessel is more easily identified in the continuation of the vessel in the adjacent field [X]. (Right) There is a large thrombus of tumor within a vascular space associated with hemorrhage and fibrin. This vessel is at the periphery of the gland, immediately below the inked margin.

Follicular Carcinoma

Vascular Invasion


(Left) There are 3 areas of vascular invasion  in this image, although, it is probably a single vessel that goes in and out of the plane of focus. When counting vascular involvement, this should be counted as 1 area of invasion. (Right) Neoplastic cells line a vascular space  within the tumor capsule. This is an oncocytic follicular carcinoma associated with a mucinous material. Mucinous material is nonspecific, as it can be seen in a wide variety of thyroid lesions.

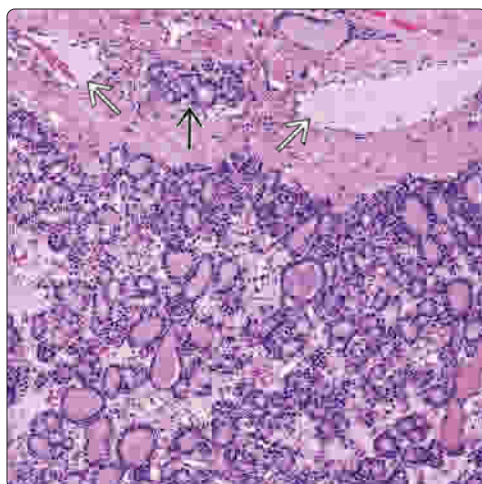


Lymphatic Invasion

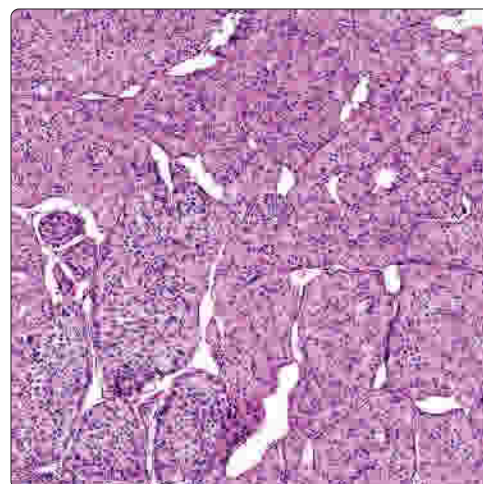


Tumor Entrapment Between Vessels


(Left) This is an example of entrapment of follicular cells  between 2 vessels. This is not invasion. There were no additional findings in this tumor, which would be diagnosed as a follicular adenoma. Entrapment is a potential pitfall in follicular tumors. (Right) A trabecular or insular pattern can be seen in follicular tumors. Invasion would need to be shown to diagnose carcinoma because a trabecular or insular pattern can be seen in many different follicular lesions.

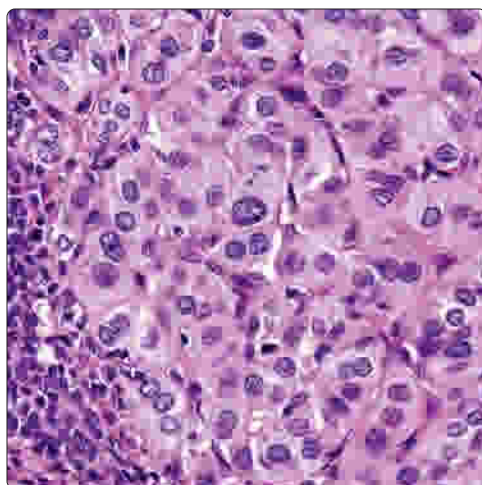


Trabecular and Insular Architecture

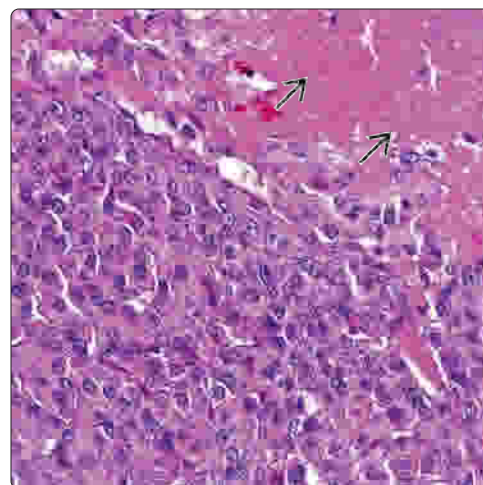


Organoid Pattern of Growth

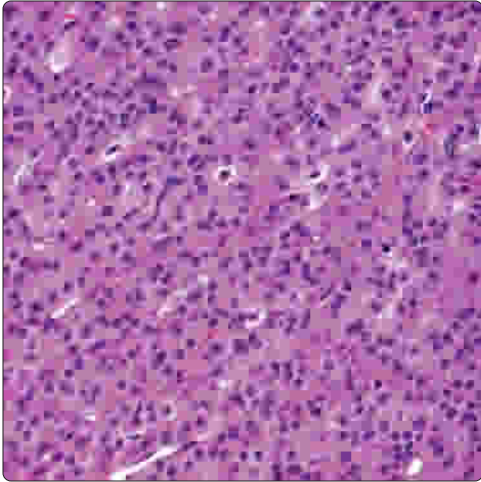
(Left) A variety of patterns of growth can be seen in follicular carcinoma. In examples like this one, an organoid pattern can mimic a medullary carcinoma. When colloid is absent, thyroglobulin is useful in confirming the nature of the process. (Right) Tumor necrosis is present  in this follicular carcinoma, although, it is an uncommon finding. Note the prominent nucleoli in nearly every tumor cell. Colloid is not identified in this field.



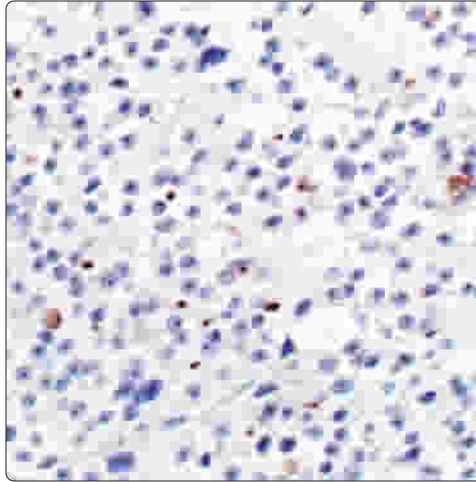
Tumor Necrosis in Follicular Carcinoma



Oncocytic Tumor With Limited Colloid

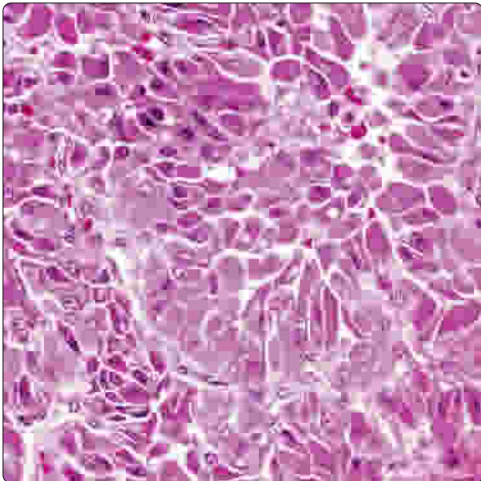


Thyroglobulin Immunoreactivity

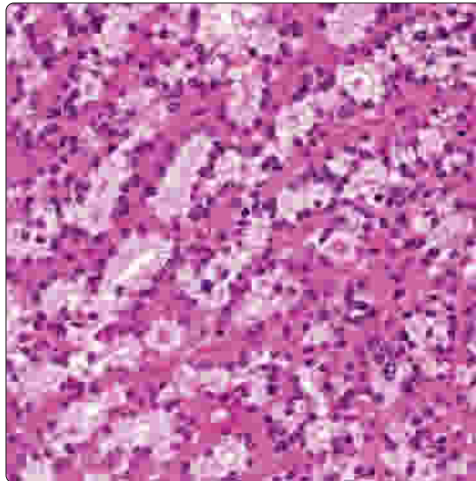


(Left) There is an oncocytic neoplastic proliferation of thyroid follicular cells in this follicular carcinoma. However, colloid is exceedingly limited. This is the type of proliferation that should have a thyroglobulin or PAS performed to confirm the presence of colloid. **(Right)** In oncocytic tumors, it is often helpful to perform a thyroglobulin immunohistochemistry, helping to confirm the follicular epithelial derivation of the neoplastic cells.

Oncocytic Cells

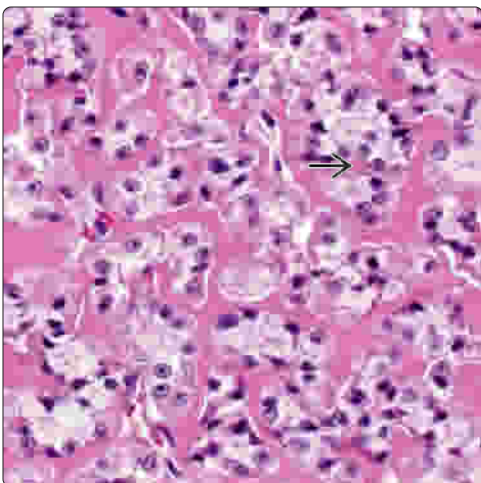


Clear Cell Change

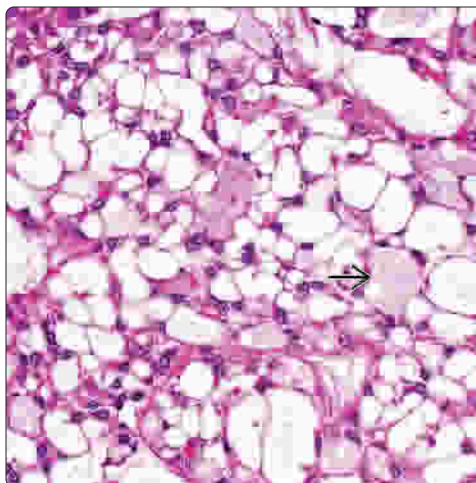


(Left) Oncocytic (oxyphilic, Hürthle) cells are large, polygonal cells with abundant, granular, brightly eosinophilic, opacified cytoplasm. The nuclear chromatin is clear to vesicular, with prominent, brightly eosinophilic, round to irregular nucleoli seen in the center. **(Right)** Clear cell change is frequently seen in oncocytic lesions but can be found on its own (signet ring variant). These inclusions are usually strongly and diffusely immunoreactive with thyroglobulin.

Clear Cytoplasm and Tumor Fibrosis




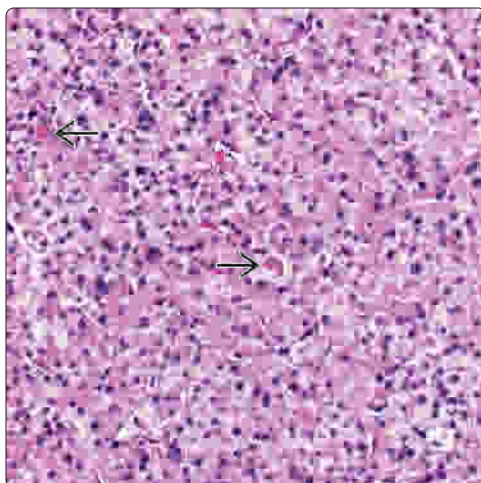
Clear Cell Change



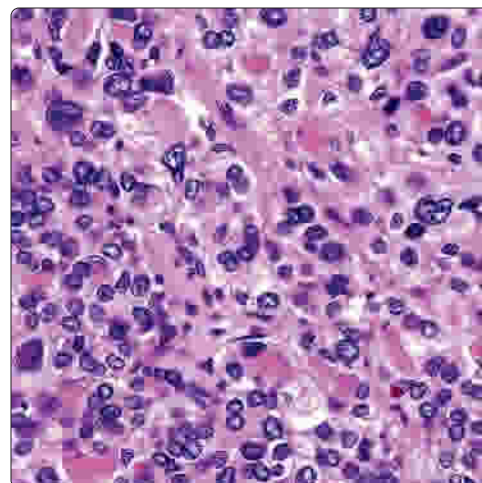
(Left) There is intratumoral fibrosis in this follicular carcinoma, showing a small, tight follicular distribution. Colloid is focally noted in tumor cells that are oncocytic to clear. **(Right)** Clear cell change creates a sieve-like appearance and focal areas of signet ring formation. There is focal colloid, helping to confirm a follicular derivation to this carcinoma. This tumor showed thyroglobulin immunoreactivity.

Oncocytic and Clear Cell Change



(Left) This follicular carcinoma shows a predominantly clear cell change, which is an artifact in an oncocytic tumor. Note the very limited colloid production . **(Right)** The nuclei of follicular carcinoma are often irregular in size and shape, but the nuclear chromatin is coarse and heavy. Colloid is present throughout the tumor.

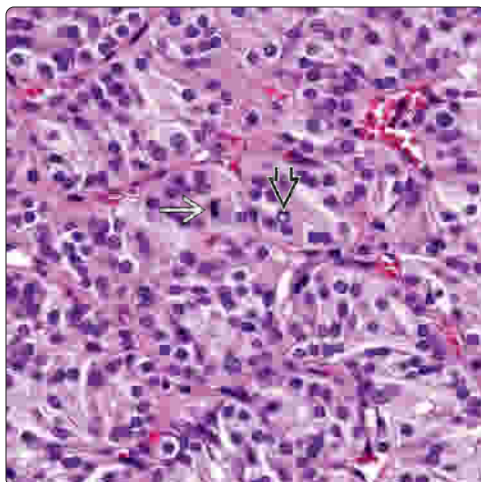


Coarse Nuclear Chromatin Distribution

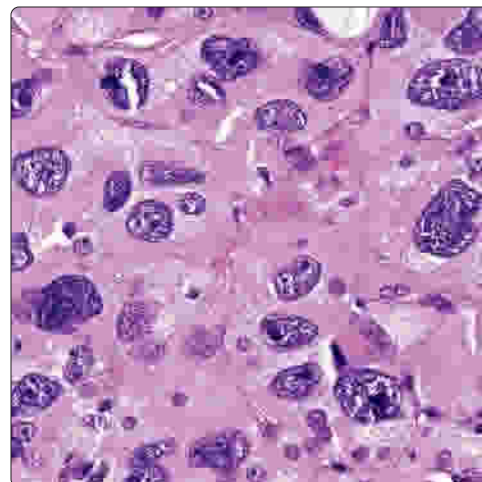


Mitotic Figure in Follicular Carcinoma

(Left) The neoplastic cells of follicular carcinoma are frequently monotonous, with a relatively low nuclear:cytoplasmic ratio. A mitotic figure is seen . There is abundant cytoplasm, which is often associated with intranuclear cytoplasmic inclusions . **(Right)** Isolated foci of remarkable pleomorphism can be seen within a follicular carcinoma. However, pleomorphism alone in endocrine organ tumors does not equate to malignancy.

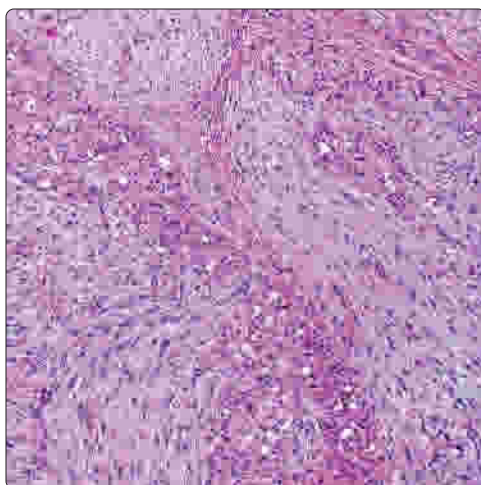


Remarkable and Profound Pleomorphism

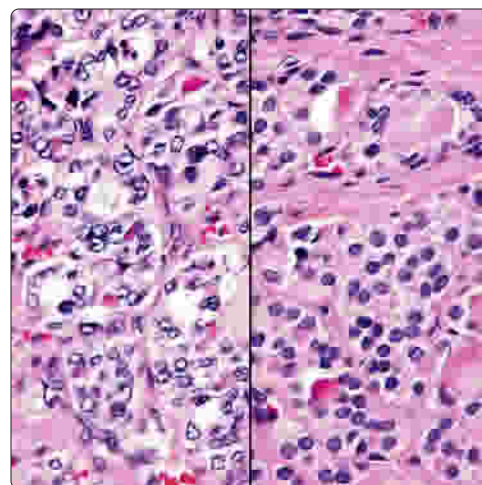


Undifferentiated Carcinoma

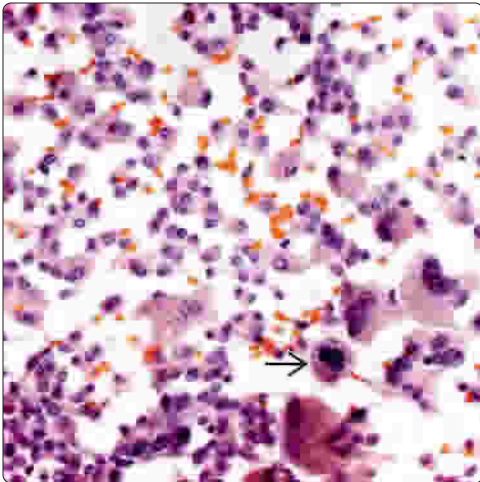
(Left) This undifferentiated carcinoma has developed in an oncocytic follicular carcinoma. Sampling of areas in the gross specimen that appear different helps to highlight these types of changes. **(Right)** Processing artifacts can frequently cause interpretation problems. Sample on the left has been processed on a heating plate for 2 hours without fresh clearing solutions (no dehydration). Sample on the right has been reprocessed without heating plate and no excess water in the solutions.



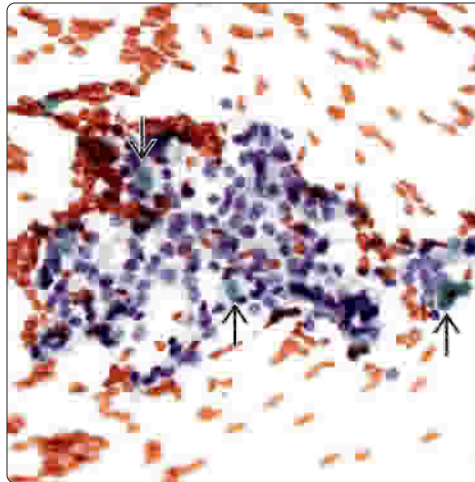
Processing Artifacts





Cellular Smears With Oncocytic Cells



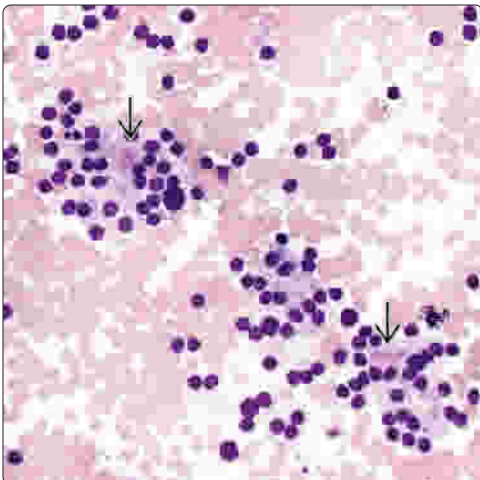
Follicular Sheets



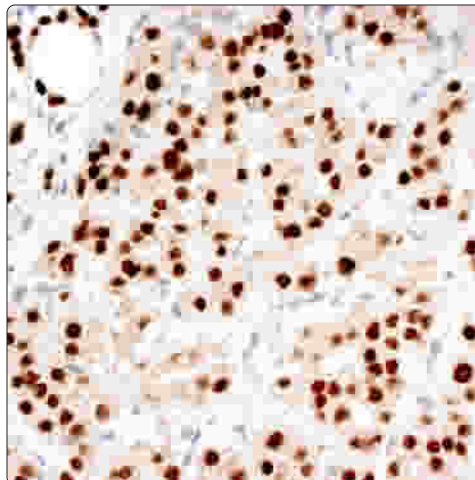
(Left) Although cytology smears are unreliable in separating benign from malignant cells, this tumor shows increased cellularity, cytoplasmic oxyphilia, and focal cellular pleomorphism. An atypical mitotic figure  suggests a tumor rather than an adenomatoid nodule.


(Right) There is a follicular epithelial sheet, showing small droplets of colloid  easily identified within the proliferation.

Follicular Epithelial Proliferation

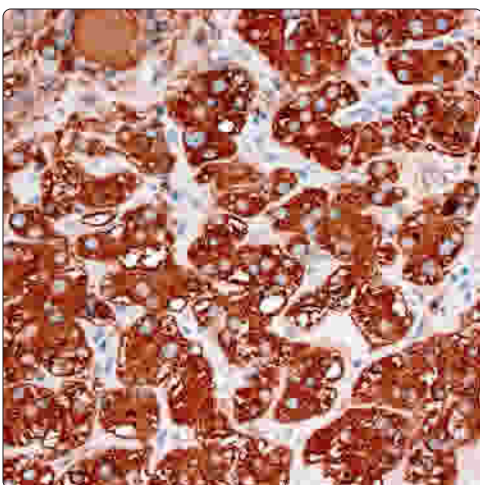


Strong Nuclear TTF-1 Reaction

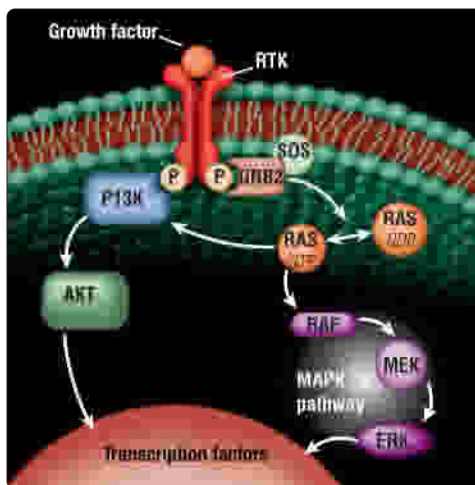


(Left) This smear shows a cellular follicular epithelial proliferation, arranged in follicles, with small droplets of colloid . This degree of cellularity and pattern is that of a follicular neoplasm (Bethesda IV). (Right) This follicular tumor showed limited colloid, so a strong TTF-1 reaction helps to confirm thyroid derivation. However, C cells and follicular epithelial cells are both TTF-1 reactive.

Strong Thyroglobulin Reactivity



MAPK and PIK3CA/AKT1 Pathways



(Left) In most follicular carcinomas, IHC is not required. Sometimes thyroglobulin may confirm follicular cell origin. (Right) RAS functions as a molecular switch propagating signals from receptor tyrosine kinases. With activation, RAS shifts from an inactive, GDP-bound to active, GTP-bound form and phosphorylates downstream cytoplasmic targets. Point mutations stabilize the protein in its active form, leading to constitutive stimulation of the MAPK and PIK3CA/AKT1 pathways.

KEY FACTS

TERMINOLOGY

- Malignant epithelial thyroid neoplasm showing histologic and biologic features intermediate between differentiated thyroid carcinomas and undifferentiated (anaplastic) carcinoma

ETIOLOGY/PATHOGENESIS

- Usually arise de novo but may transform from differentiated thyroid carcinomas (e.g., papillary or follicular carcinoma)

CLINICAL ISSUES

- At presentation, often locally advanced disease with extrathyroidal extension
- Multimodality therapy including: Total thyroidectomy, neck dissection for patients with lymph node disease, and postoperative radioactive iodine
- Death from disease is common but does not follow rapid demise as in undifferentiated (anaplastic) carcinoma
 - 5-year survival rate of 50-72%

- 10-year survival rate of 46%





MICROSCOPIC

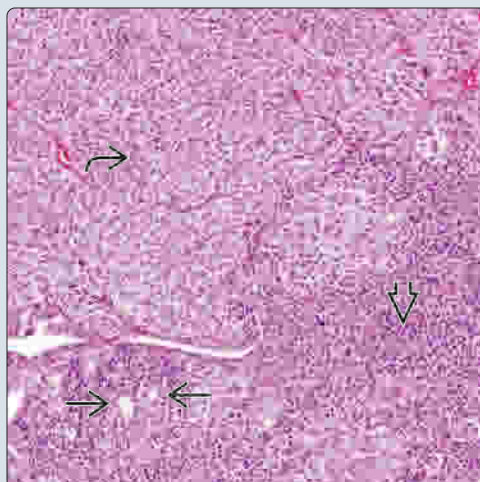
- Diagnosis of poorly differentiated thyroid carcinoma (PDTc) predicated on Turin proposed criteria including
 - Presence of solid, trabecular, insular pattern of growth
 - Mitotic activity ≥ 3 per 10 HPF
 - Tumor necrosis (coagulative type)
 - Convoluted nuclei

ANCILLARY TESTS

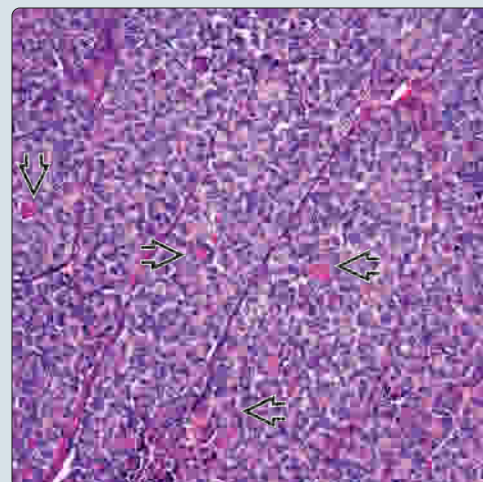
- Thyroglobulin (+)
 - Variable (cytoplasmic) staining from case to case and even within same case including
 - Paranuclear globular staining pattern may be present
- TTF-1 (+)
 - Tends to be diffuse and strong (nuclear) staining
- Pax-8 (nuclear) staining
- Cytokeratins (AE1/AE3, CAM5.2, CK7) (+)

Insular and Diffuse Growth



(Left) Poorly differentiated thyroid carcinoma (PDTc) is characterized by varied growth patterns that may include insular (organoid, cell nest)  separated by fibrovascular stroma and diffuse (solid, sheet-like) . Follicular pattern growth is identified , although the follicles lack colloid. **(Right)** In addition to insular (organoid) and diffuse growth, trabecular pattern growth may be present to include identifiable colloid-filled follicles .

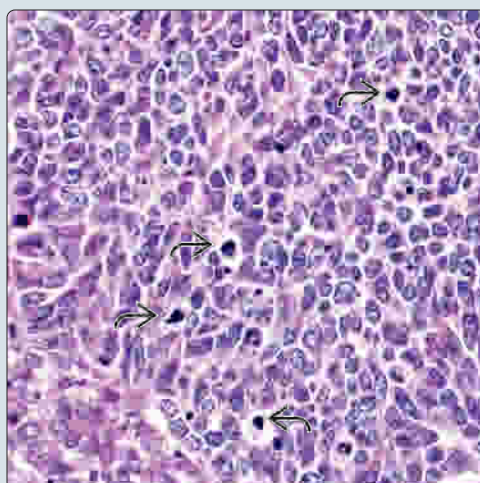


Trabecular Growth

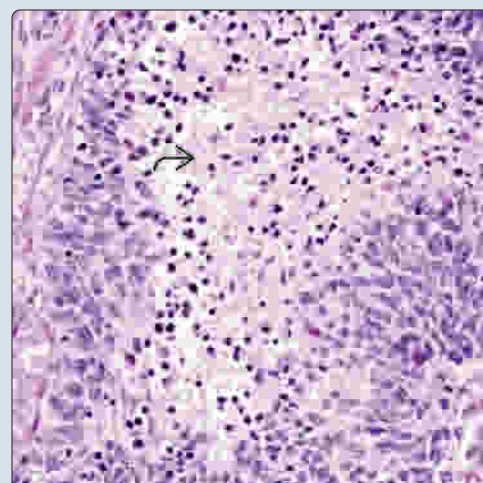


Increased Mitotic Activity

(Left) PDTc is characterized by diffuse (sheet-like) growth, cells with hyperchromatic to vesicular nuclei with moderate nuclear pleomorphism, and increased mitotic activity  of > 3 mitoses per 10 HPF. **(Right)** Coagulative necrosis is identified . The diagnosis of PDTc can be made in a thyroid neoplasm with increased mitotic activity and foci of necrosis irrespective of the growth patterns (e.g., insular). Insular growth may be seen in benign thyroid tumors and differentiated thyroid carcinomas.



Coagulative Necrosis



TERMINOLOGY

Abbreviations

- Poorly differentiated thyroid carcinoma (PDTC)

Synonyms

- Insular carcinoma

Definitions

- Malignant epithelial thyroid neoplasm showing histologic and biologic features intermediate between differentiated thyroid carcinomas and undifferentiated (anaplastic) carcinoma

ETIOLOGY/PATHOGENESIS

Idiopathic

- Usually arise de novo
- May be associated with transformation from differentiated thyroid carcinomas (e.g., papillary or follicular carcinoma)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon in USA, representing < 2% of all thyroid cancers
 - Mountain region of Northern Italy represents 4-7% of all thyroid malignant neoplasms
- Age
 - Most common in 6th decade
 - Typically occurs decade later than differentiated thyroid cancers
 - May occur in children, but this is rather rare
- Sex
 - Female > male

Site

- Anywhere in thyroid gland without specific localization

Presentation

- Thyroid mass of varying duration
 - Some are of recent duration (within 1 year); others occur in longstanding enlarged thyroid (i.e., goitrous thyroid gland)
 - Rarely, patients present with distant metastasis
 - At presentation, often (but not always) associated with locally advanced disease, including extrathyroidal extension

Laboratory Tests

- Patients are usually euthyroid

Treatment

- Options, risks, complications
 - Multimodality therapy including: Total thyroidectomy, neck dissection for patients with lymph node disease, and postoperative radioactive iodine
 - Advocated for all patients owing to high mortality rates; however, conflicting data in literature on avidity for radioactive iodine
 - Conflicting data in literature on avidity of PDTC for radioactive iodine

- Adjuvant external beam radiation advocated for patients with
 - T3 tumors without distant metastases
 - T4 tumors
 - Unresectable or incompletely excised tumors
 - Locoregional recurrence
 - Regional lymph node metastases

Prognosis

- Death from disease is common
 - Caused by uncontrolled local or distant metastatic disease
 - In contrast to rapid demise typically associated with undifferentiated (anaplastic) carcinoma, death from PDTC occurs after several years
 - 5-year survival rate of 50-72%
 - 10-year survival rate of 46%
- Recurrence and metastasis following treatment occur in high proportion of cases (> 60%)
 - Lymph node and distant metastases occur in ~ 60-70% of cases, respectively
- Prognosis associated with worse outcome includes
 - Patients ≥ 45 years of age
 - Tumor measuring > 4 cm (decreased progression-free survival)
 - Presence of extrathyroidal extension into perithyroidal soft tissues (correlates with decreased overall survival)
 - Presence of metastasis
 - RAS mutation
 - Presence of insulin-like growth factor II messenger RNA protein-3 (IMP3) immunoreactivity
- Noninvasive (encapsulated) PDTC
 - Significantly improved overall survival compared to invasive tumors
 - Indolent behavior even in presence of extensive tumor necrosis

IMAGING

General Features

- Appear as cold nodule on thyroid scanning
 - Owing to loss of avidity for radioiodine, tumor may not be detected on scanning but may require FDG PET

MACROSCOPIC

General Features

- Solid, firm, and tan-white with associated hemorrhage and necrosis
- Typically overtly infiltrative with extrathyroidal extension but may be encapsulated (partly or completely)

Size

- Vary in size (1-10 cm) but most measure > 5 cm

MICROSCOPIC

Histologic Features

- Diagnosis of PDTC predicated on Turin proposed criteria including
 - Presence of solid, trabecular, insular pattern of growth

- Growth pattern alone (e.g., insular, solid, trabecular, others) not defining criteria for classifying thyroid tumor as poorly differentiated
 - Benign tumors and differentiated thyroid carcinomas may show insular, solid, and trabecular growth; generally lack increased mitotic activity and necrosis
- Presence of at least 1 of the following features
 - Mitotic activity ≥ 3 per 10 HPF
 - Tumor necrosis
 - Convoluting nuclei
- Absence of conventional nuclear features of papillary thyroid carcinoma
- Growth patterns
 - Dominant growth patterns include insular, trabecular, solid
 - Insular growth characterized by well-defined cell nests surrounded by thin fibrovascular septa
 - Nests are predominantly solid growth \pm microfollicles
 - Trabecular growth characterized by cells arranged in cords or ribbons
 - Solid growth characterized by sheets of neoplastic cells
 - Follicular pattern growth \pm colloid may be identified
 - Colloid may appear drop-like
- Cytomorphology
 - Monotonous population of small cells with convoluted nuclei characterized by hyperchromatic, raisin-like nuclei, indistinct to small nucleoli, and indistinct cytoplasm
 - Some irregularities in nuclear contour may be present but there is absence of nuclear features diagnostic for papillary thyroid carcinoma
 - Cells with larger nuclei, vesicular nuclear chromatin, smooth nuclear contours, and identifiable nucleoli may be identified
- Mitotic activity
 - Turin criteria is ≥ 3 per 10 HPF
 - ≥ 5 mitoses per 10 HPF proposed in criteria associated with thyroid carcinomas with high-grade features
 - Atypical mitoses can be seen
- Necrosis commonly identified
 - Represents coagulative-type necrosis involving groups of tumor cells and not individual cell necrosis
 - May be focal, appearing as small foci in center of solid nests or insulae
 - May be more extensive, appearing as confluent foci in this setting; may spare areas around blood vessels; creating peritheliomatous appearance
- Invasiveness
 - Most PDTCs are extensively invasive, including
 - Intrathyroidal invasion with capsular invasion, vascular invasion, and invasion into adjacent thyroid parenchyma
 - Extrathyroidal extension
 - May be noninvasive, referred to as noninvasive PDTC, characterized by
 - Encapsulated tumor with high-grade features (necrosis and increased mitotic activity) without evidence of invasion
- Entire tumor should be submitted to exclude presence of invasion
- Amount of poorly differentiated foci for diagnosis of PDTC
 - Presence of minor component of poorly differentiation features in differentiated thyroid carcinomas shown to portend more aggressive features
 - In some studies, $< 20\%$ poorly differentiated foci shown to affect prognosis significantly
 - In other studies, $\geq 10\%$ poorly differentiated foci shown to affect prognosis significantly
- Other cell types that may be seen in PDTC include
 - Oncocytic cells
 - Rhabdoid cells
 - Cells with hobnail features reported in association with PDTC, suggesting that hobnail features may be manifestation of higher grade transformation

ANCILLARY TESTS

Cytology

- High cellularity
- Large sheets of tumor cells showing microfollicular pattern or smaller sheets with insular, solid, or trabecular patterns
- Cellular aspirates composed of dyscohesive, small, monotonous, round to oval cells with
 - High nuclear:cytoplasmic ratio, severe crowding, nuclear hyperchromasia, coarsely or finely granular chromatin, small nucleoli, poorly outlined cytoplasm
 - Very scanty colloid
 - Necrosis and mitotic figures may or may not be identified

Immunohistochemistry

- Thyroglobulin (+)
 - Variable (cytoplasmic) staining from case to case and even within same case, including
 - Very focal limited to abortive or small follicles containing colloid
 - Limited to isolated cells as paranuclear globules or vacuoles
 - Completely negative
 - Positive foci adjacent to negative foci
 - Staining typically not diffusely/strongly reactive
- TTF-1(+)
 - Tends to be diffuse and strong (nuclear) staining
- Pax-8 (nuclear) staining
- Cytokeratins (AE1/AE3, CAM5.2, CK7) (+)
- Calcitonin and neuroendocrine markers (chromogranin, synaptophysin, CD56) typically negative
- Ki-67 (MIB-1) shows high proliferative index
- p53 reactivity (focal or diffuse)
- Rhabdoid cells (-) for thyroglobulin but are vimentin (+) owing to presence of intermediate filaments

Genetic Testing

- β -catenin gene mutation (*CTTNB1*) may be identified
- Point mutations of *RAS* oncogene in significant proportion of cases
- *BRAF* mutations uncommon unless arising in association with PTC
- *RET/PTCH1* or *NCOA4* rearrangement uncommon
- *PAX8/PPARG* rare

- Telomerase reverse transcriptase (*TERT*) promoter mutations identified
 - Associated with more aggressive-behaving thyroid cancers
- *PIK3CA*, *PTEN*, and *CDKI* mutations present in 14-20% of PDTCs

DIFFERENTIAL DIAGNOSIS

Undifferentiated (Anaplastic) Thyroid Carcinoma

- Rapidly enlarging neck or thyroid mass occurring over short periods of time (weeks to months)
- Growth patterns include solid, fascicular, and storiform
- Most common cell types include spindle-shaped (sarcomatoid)
- Neoplastic infiltrate is undifferentiated without evidence of colloid formation as is present in PDTC
- Immunohistochemistry
 - Cytokeratin and Pax-8 (nuclear) expression
 - Most useful marker with reactivity identified in majority of cases
 - Thyroglobulin and TTF-1 reactivity extremely variable, usually absent, generally not helpful in diagnosis
- Extremely high mortality rates, usually over short periods of time irrespective of therapy

Papillary Thyroid Carcinoma, Solid Variant

- Shows constellation of nuclear alterations diagnostic for papillary thyroid carcinoma
- Diffuse thyroglobulin reactivity

Medullary Thyroid Carcinoma

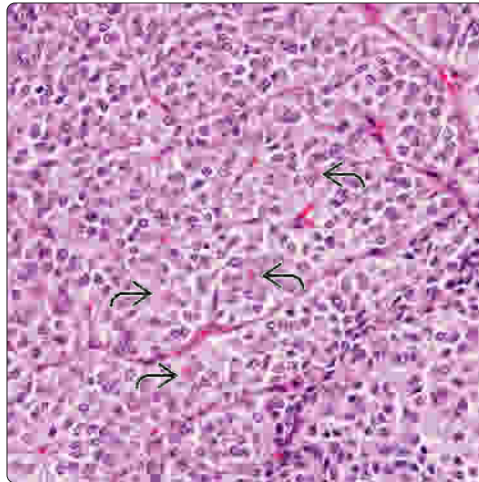
- Growth patterns may include insular, trabecular, solid
- May have increased mitotic activity and necrosis
- Shows characteristic nuclear chromatin (stippled or salt and pepper)
- Immunoreactive for calcitonin, neuroendocrine markers (chromogranin, synaptophysin, others), TTF-1, cytokeratins
- Thyroglobulin (-)

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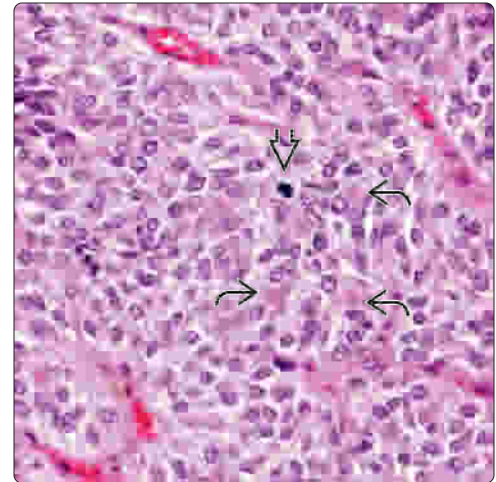
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(Left) Insular or organoid growth composed of nests is separated by fibrovascular stroma. The neoplastic cells are rather monotonous appearing with scattered microfollicles containing identifiable, drop-like colloid [A]. **(Right)** Monotonous cell population with identifiable microfollicles containing drop-like colloid [B] is shown; a mitotic figure is present [C]. The presence of colloid may be easily overlooked.

Scant Colloid

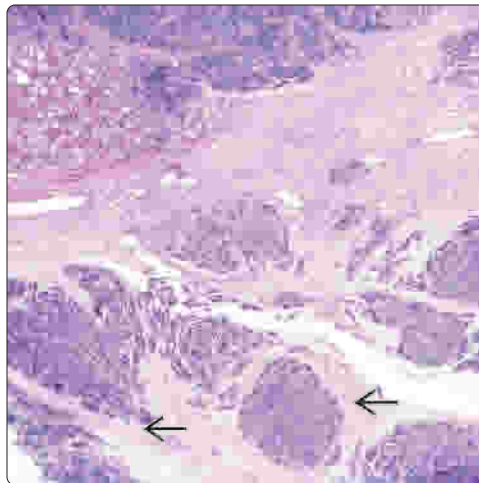


Colloid Present With Mitoses

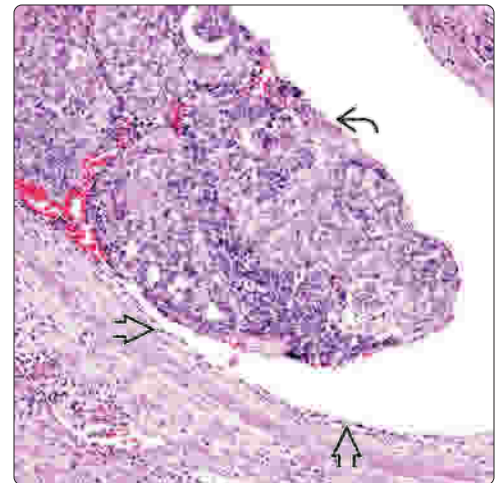


(Left) Most cases of PDTC show the presence of carcinoma outside the confines of the thyroid gland [A], although rare examples may be encapsulated without invasion beyond its capsule. **(Right)** Invasive growth is often present, including vascular invasion characterized by tumor invading into endothelial-lined [B] vascular spaces with focal fibrin thrombus formation [C]. In addition, there is often extensive intrathyroidal and extrathyroidal invasion (not shown).

Extrathyroidal Extension

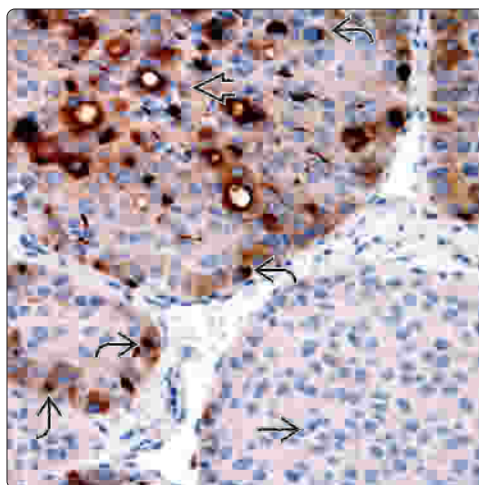


Vascular Invasion

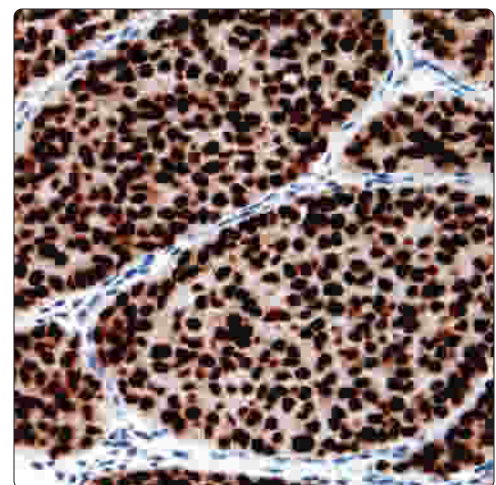


(Left) Variable thyroglobulin immunoreactivity is present, including tumor nests with thyroglobulin staining [A] adjacent to tumor nests without thyroglobulin reactivity [B]. Dot-like paranuclear thyroglobulin staining is present [C], a feature seen in PDTC. **(Right)** Diffuse TTF-1 (nuclear) immunoreactivity is present. In contrast, undifferentiated (anaplastic) thyroid carcinoma typically does not express immunoreactivity for thyroglobulin and TTF-1.

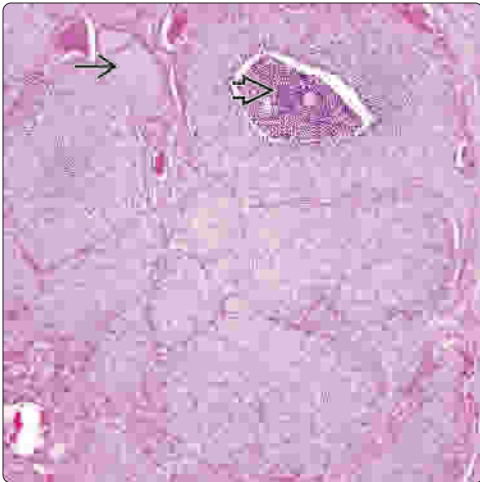
Variable Thyroglobulin Reaction



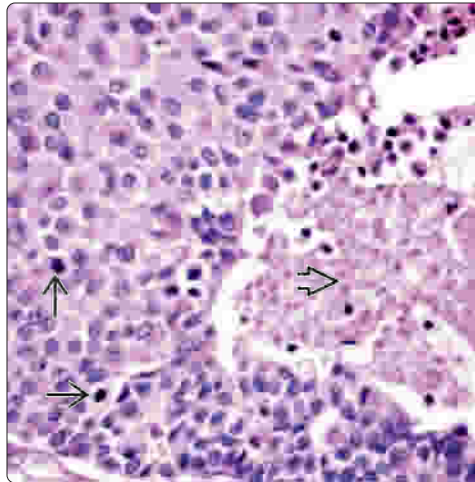
Strong TTF-1 Reaction



Medullary Thyroid Carcinoma

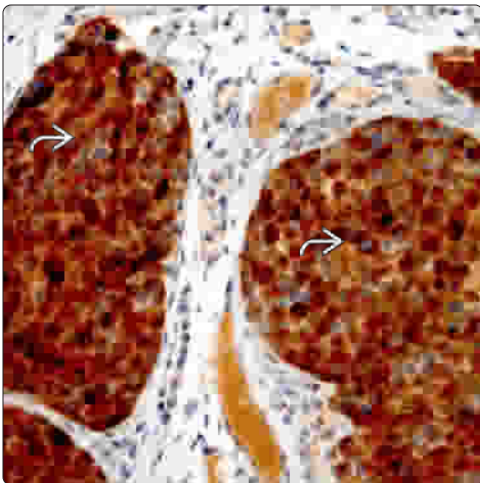


Necrosis in Medullary Carcinoma

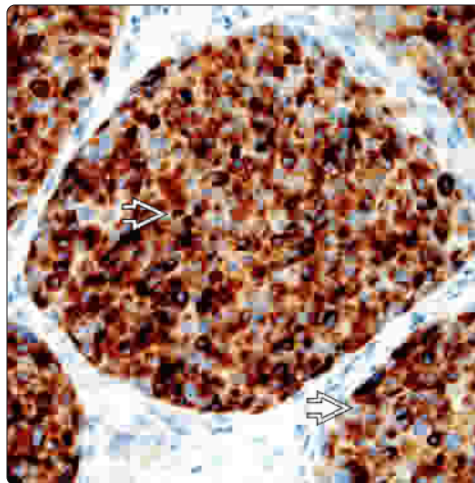


(Left) In addition to undifferentiated (anaplastic) thyroid carcinoma, the differential diagnosis for PDTC may include medullary thyroid carcinoma (MTC), which shows insular (cell nest) growth and foci of necrosis [1]. Intervening nonneoplastic, colloid-filled follicles are present [2]. (Right) MTC may include rather monotonous-appearing cell population with dispersed nuclear chromatin, absence of colloid, increased mitotic activity [3], and necrosis [4] suggesting a possible diagnosis of PDTC.

Medullary Thyroid Carcinoma and Calcitonin

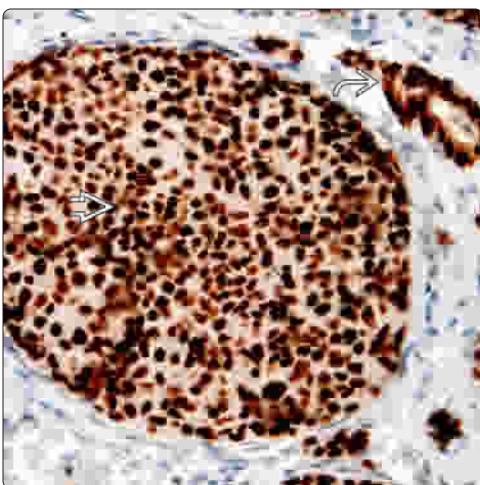


Medullary Thyroid Carcinoma and Chromogranin

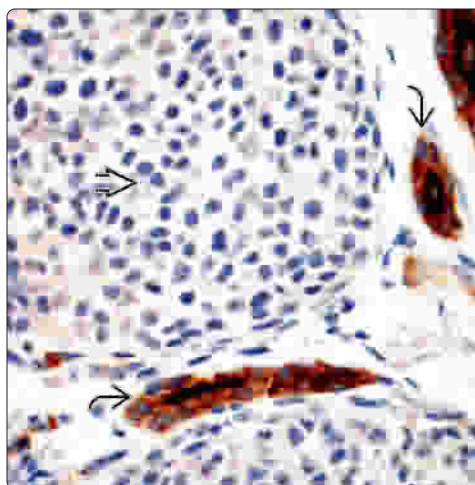


(Left) The neoplastic cells of MTC typically are diffusely calcitonin positive [5]. (Right) The neoplastic cells of MTC are reactive for neuroendocrine markers, including chromogranin [6], as well as synaptophysin (not shown). Like PDTC, MTC will be immunoreactive for cytokeratins (not shown). The presence of calcitonin and neuroendocrine markers are diagnostic for MTC and differentiates it from PDTC.

Medullary Thyroid Carcinoma and TTF-1



Medullary Thyroid Carcinoma and Thyroglobulin



(Left) MTCs are (diffusely) immunoreactive for TTF-1 (nuclear) [7]. Cytokeratins and TTF-1 immunoreactivity is present in MTC and PDTC and does not assist in differentiating these tumors. Note TTF-1 reactivity in benign thyroid follicles [8]. (Right) MTCs lack thyroglobulin immunoreactivity [9], but it is present in benign thyroid follicles [10]. While the expression of thyroglobulin may be variable in PDTC, it is usually at least focally present.

KEY FACTS

TERMINOLOGY

- Highly aggressive malignant thyroid neoplasm composed of undifferentiated cells that exhibit immunohistochemical or ultrastructural epithelial differentiation

ETIOLOGY/PATHOGENESIS

- Preexisting benign or malignant thyroid disease in nearly all cases

CLINICAL ISSUES

- Elderly, with vast majority > 65 years at diagnosis
- Rapidly expanding neck mass in patient with long history of thyroid disease
- Multimodality therapy required
- Grave overall prognosis: > 95% die from disease; median survival: 3 months

MACROSCOPIC

- Fleshy to firm mass, typically completely replacing thyroid parenchyma; mean: 6 cm

MICROSCOPIC

- Extrathyroidal extension, lymph-vascular invasion, significant necrosis, and hemorrhage
- Variety of patterns: Sheet-like, storiform, fascicular, angiomatoid, meningothelial
- Poorly differentiated cells, polygonal, pleomorphic, spindle, giant, epithelioid, squamoid
- Profound pleomorphism
- Increased mitotic figures, including atypical forms, and pyknotic cells

ANCILLARY TESTS

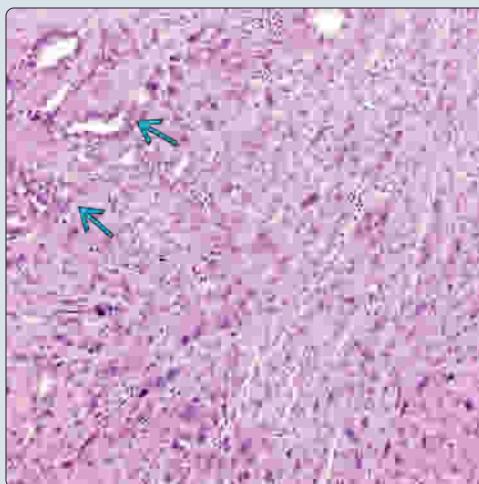
- Cytokeratins and pax-8 (nuclear) in up to 80% of cases
- Thyroglobulin and TTF-1 are usually lost

TOP DIFFERENTIAL DIAGNOSES

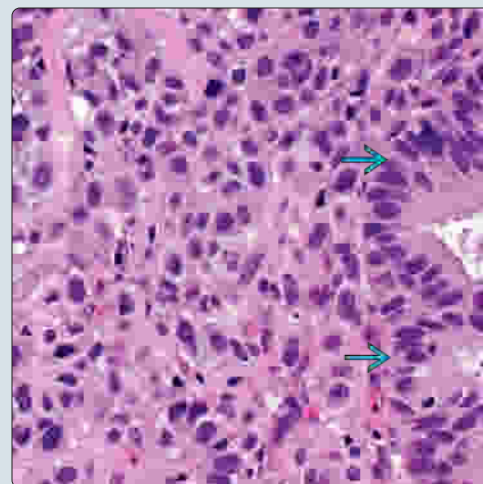
- Metastases, primary or secondary sarcoma, melanoma, lymphoma, primary differentiated carcinomas, Riedel thyroiditis (IgG4 sclerosing disease)

(Left) There is a small residuum of papillary carcinoma that has undergone malignant transformation to a spindled cell undifferentiated carcinoma. **(Right)** There is a pleomorphic epithelial proliferation immediately adjacent to a papillary carcinoma. This is a typical appearance for an undifferentiated carcinoma of the thyroid.

Papillary and Undifferentiated Carcinoma

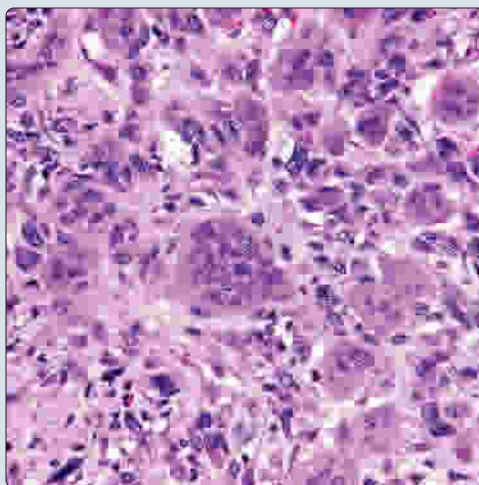


Pleomorphic Epithelial Neoplasm

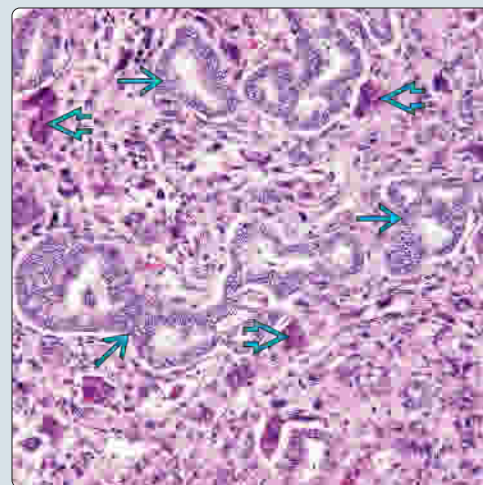


(Left) Osteoclastic-type giant cells are seen in some undifferentiated carcinomas. The nuclei are relatively bland, aggregated within the cell. These cells are CD68-positive histiocytes. The malignant part is between these cells. **(Right)** There are isolated areas of papillary carcinoma juxtaposed to the pleomorphic proliferation. A number of osteoclastic-type giant cells are also present. The tumor is spindled to epithelioid.

Osteoclastic-Type Giant Cell Pattern



Classical Papillary Carcinoma With Undifferentiated Carcinoma



TERMINOLOGY

Synonyms

- Anaplastic carcinoma
- Dedifferentiated carcinoma
- Spindle and giant cell carcinoma; sarcomatoid carcinoma; pleomorphic carcinoma; metaplastic carcinoma; carcinosarcoma

Definitions

- Highly aggressive malignant thyroid neoplasm composed of undifferentiated cells that exhibit immunohistochemical or ultrastructural epithelial differentiation

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Radiation
 - ~ 10% of patients report radiation exposure
- Iodine deficiency (for at least 20 years)

Thyroid Disease

- Preexisting benign or malignant thyroid disease in nearly all cases
 - Longstanding goiter (nodules)
 - Often decades
 - Constant stimulation improves odds of transformation
- Transformation (dedifferentiation) of preexisting differentiated carcinoma
 - Papillary, follicular, or poorly differentiated carcinoma
 - Identified in up to 80% of undifferentiated carcinoma (UC)
 - Papillary carcinoma is most common (80%)

Pathogenesis

- Thyroid follicular epithelial cell origin, often difficult to prove

CLINICAL ISSUES

Epidemiology

- Incidence
 - Represents ~ 2% of all thyroid gland malignancies
 - ~ 1-2/1,000,000 population annually
 - Higher in endemic goiter regions (iodine deficiency), Europe, and low socioeconomic status
- Age
 - Elderly, with vast majority > 65 years at diagnosis
- Sex
 - Female > male (1.5:1)

Site

- Most are single (60%) lobe tumors
- Multifocal (40%) or bilateral (25%)

Presentation

- Rapidly expanding neck mass
 - Exceedingly fast tumor doubling: 1-2 weeks
 - Fixed and hard mass
- Usually long history of thyroid disease
- Hoarseness, dysphagia, vocal cord paralysis, cervical pain, and dyspnea are common

- Invades into soft tissues (muscle, fat, and nerves), esophagus, trachea
- Lymphadenopathy is common
- Hyperthyroidism is uncommon; results from rapid destruction of follicles with hormone release

Laboratory Tests

- Leukocytosis can be seen (secretion of macrophage colony-stimulating factor)

Treatment

- Surgical approaches
 - Value of surgery is yielding diagnostic material and palliation
 - Debulking, as resectability is unlikely
 - May be valuable in limited disease cases
- Adjuvant therapy
 - Combination chemotherapy (doxorubicin, cisplatin), although poor response
 - Targeted therapies show promise: Proteasome inhibitors, multikinase inhibitors, vascular targeting agents, and gene therapies
 - Gefitinib (EGFR inhibitor); bevacizumab (antibody against VEGF-R); combretastatin-A4 (fosbretabulin) vascular-disrupting agent (best in younger patients)
 - Multikinase-targeted inhibitors
 - ◻ Mutations of *BRAF*, *PTEN*, and *PIK3CA* genes are common, with *RAS* and *TP53* most frequent
 - ◻ Sorafenib (Nexavar) is multikinase inhibitor
- Radiation
 - Radiation (external beam, 3D conformal therapy, intensity modulated radiotherapy)
 - Hyperfractionation or accelerated dosing regimens improves efficacy
 - Rapid doubling rate requires accelerated dosing
- Multimodality therapy required

Prognosis

- Rapidly progressive local disease
- Many patients have lymph node disease at presentation
 - Up to 50% cervical adenopathy
- Metastases to distant sites common
 - Up to 50% at presentation: Lungs (50%), bones (15%), brain (10%)
- Grave overall prognosis
 - > 95% die from disease; median survival: 3 months
- Better prognosis in cases where anaplastic carcinoma is confined to encapsulated tumor or minor component of another tumor
- Worse prognosis: > 60 years, male, > 5 cm, extensive local disease

IMAGING

General Features

- CT shows extent of disease
- Infiltrative (carotid and internal jugular) heterogeneous mass with irregular borders, necrosis, and sometimes calcifications

MACROSCOPIC

General Features

- Fleshy to firm mass, typically completely replacing thyroid parenchyma
- Infiltrative with irregular borders
 - Extrathyroidal extension: Soft tissue, larynx, trachea, esophagus, lymph nodes
- Pale, white-tan, brown
- Commonly variegated, with areas of necrosis and hemorrhage

Sections to Be Submitted

- Adequate sampling required to find preexisting or coexisting carcinoma

Size

- Range: 1-20 cm; mean: 6 cm

MICROSCOPIC

Histologic Features

- Up to 50% of tumors show extrathyroidal extension
 - Local extension into soft tissues or other organs
 - Effacement of thyroid parenchyma
- Extensive lymph-vascular invasion
 - Vessel walls invaded or colonized and destroyed
- Significant coagulative-type necrosis, hemorrhage, and degeneration
- Colloid is absent, but entrapment of follicles can be seen at periphery
- Desmoplastic stroma may be present
- Variety of patterns: Sheet-like, storiform, fascicular, angiomatoid, meningothelial
- Poorly differentiated, profoundly pleomorphic cells
 - Polygonal, pleomorphic, spindle, giant, epithelioid, squamoid
 - Noticeable variation within tumors and between cases
- Tumor giant cells and osteoclast-like giant cells are common
- Increased mitotic figures, including atypical forms, and pyknotic cells
- Prominent acute inflammatory infiltrate may be present

Variants

- **Spindle cell variant**
 - Most common variant, with high-grade sarcoma pattern (fascicles, storiform)
- **Pleomorphic giant cell variant**
 - 2nd most common, comprised of sheets of profoundly pleomorphic/bizarre cells, often multinucleated, with intracytoplasmic hyaline globules
- **Squamoid variant**
 - Tumor shows nests and sheets of squamoid cells associated with desmoplastic stroma
 - Cytoplasm is dense, opacified, and eosinophilic, occasionally show intercellular bridges and dyskeratosis
- **Osteoclastic variant**
 - Large numbers of multinucleated, nonneoplastic, osteoclast-like giant cells (CD68-positive histiocytes)
- **Angiomatoid variant**

- Anastomosing vascular spaces, branching staghorn or hemangiopericytoma-like pattern, including erythrocyte extravasation
- **Carcinosarcoma variant**
 - Carcinoma and sarcoma combined (osteosarcoma or chondrosarcoma most common)
- **Paucicellular variant**
 - Decreased cellularity with increased fibrosis and inflammation (mimic of Riedel thyroiditis)
 - Highly atypical single spindled cells
- **Rhabdoid variant**
 - Cells with dense hyaline-type cytoplasm causing eccentric nucleus placement

ANCILLARY TESTS

Cytology

- Highly cellular with single cells, clusters, or sheets
- Marked nuclear pleomorphism, including squamoid, giant cell, and spindle cell, with ample cytoplasm
- Bizarre, single or multiple nuclei with prominent nucleoli
- Mitotic figures easily identified
- Background of necrotic debris and neutrophils
 - Colloid is usually absent
- Sometimes differentiated component may be present (dual-cell pattern)

Immunohistochemistry

- Cytokeratins and pax-8 (nuclear) in up to 80% of cases
- Thyroglobulin and TTF-1 are usually lost
- **Negative:** Myogenin, MYOD1, smooth muscle actin, FVIIIIRAg, CD31, HMB-45, Melan-A, CD45RB, ALK

Genetic Testing

- Complex and progressive accumulation of chromosomal alterations (numerical and structural aberrations)
- Mutations can be seen in differentiated and dedifferentiated tumors (*BRAF*, *RAS*)
 - Early events in thyroid tumorigenesis, predisposing to additional events leading to undifferentiated transformation
 - *RAS* seen in up to 60% of tumors
 - Present in differentiated and undifferentiated portions
 - *BRAF* seen in about 25% of tumors
 - Papillary carcinoma can usually be found
 - Present in differentiated and undifferentiated portions
- Most common in undifferentiated tumors: *TP53* and *CTNNB1*
 - *TP53* (up to 80% of tumors) but only in undifferentiated part
 - *CTNNB1* (up to 65% of tumors)
 - Accumulates in nucleus due to altered degradation
 - *PTEN* and *PIK3CA* mutations

DIFFERENTIAL DIAGNOSIS

Metastases

- Biopsy of undifferentiated tumor, clinical history, and radiographic information helps make separation

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CK-PAN	Positive	Cytoplasmic	80% of cases; limited to focal, often weak
AE1/AE3	Positive	Cytoplasmic	Best result of keratins
CK8/18/CAM5.2	Positive	Cytoplasmic	Similar results to AE1/AE3
pax-8	Positive	Nuclear	Up to ~ 80% of cases
p63	Positive	Nuclear	Up to ~ 70% of cases
EMA	Positive	Cytoplasmic	30-50% of cases, often weak and focal
Vimentin	Positive	Cytoplasmic	Strong, diffuse reaction
p53	Positive	Nuclear	Strong, diffuse nuclear reaction
CEA-M	Positive	Cytoplasmic	Usually in squamoid areas; ~ 10% of cases
TTF-1	Negative		Usually lost in dedifferentiated tumor
Thyroglobulin	Negative		Usually lost in dedifferentiated tumor
Ki-67	Positive	Nuclear	Usually high index (~ 50%)

- Metastatic carcinomas to thyroid gland: Poorly differentiated carcinoma from distant site (lung, colon, breast, gastrointestinal system)
- Pertinent immunohistochemical panel often helps

Primary/Metastatic Sarcoma

- Primary thyroid sarcomas
 - Leiomyosarcoma, angiosarcoma, malignant peripheral nerve sheath tumor, synovial sarcoma
 - Patterns of growth, cytologic appearance, immunohistochemistry, and molecular studies valuable

Melanoma (Metastatic)

- Pigmentation helps
- Positive:** S100 protein, SOX10, HMB-45, Melan-A, tyrosinase
- Frequently **positive:** *BRAF* and *NRAS* mutations

Lymphoma

- Diffuse large B-cell lymphoma most common
- Positive:** CD45RB, CD20, plus other hematologic markers

Thyroid Differentiated Carcinomas

- In tumor showing differentiated and undifferentiated foci, use undifferentiated diagnosis
- May show areas of transition from one to other
- Poorly differentiated carcinoma**
 - Solid, trabecular, or insular growth of monotonous, nonpleomorphic cells, showing increased mitoses (> 4/10 HPFs) and necrosis
 - Positive:** TTF-1, thyroglobulin, pax-8
- Medullary thyroid carcinoma**
 - Young patients, often with bilateral tumors
 - Positive:** Calcitonin, CEA; *RAS* mutations
- Spindle epithelial tumor with thymus-like differentiation (SETTLE)**
 - Spindled pattern, younger patients, lacks pleomorphism, increased mitoses, and necrosis
- Carcinoma with thymus-like elements (CASTLE)**
 - Typically shows squamoid appearance within lobular or nested growth separated by fibrous stroma, lacking significant atypia; CD5(+)

Riedel Thyroiditis (IgG4 Sclerosing Disease)

- Storiform, heavy fibrosis, inflammation, and vasculitis (obliterative phlebitis) without cellular atypia

STAGING

Definition

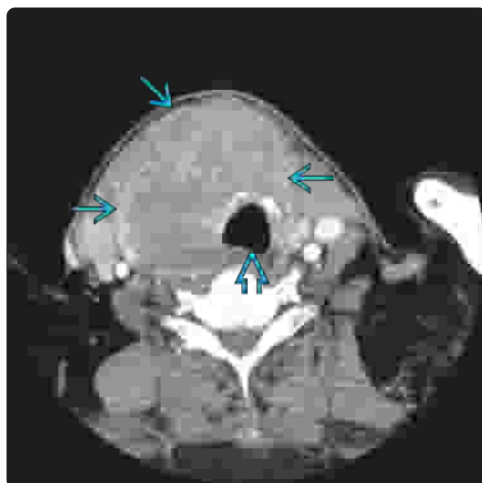
- All are T4 tumors by definition
 - T4a: Intrathyroidal tumor
 - T4b: Gross extrathyroid extension
- IVA, IVB, and IVC (latter with distant metastases)

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Large Heterogeneous Neck Mass

(Left) There is a large mass seen here that is almost entirely replacing the right thyroid lobe and expanding out into adjacent soft tissue [1]. Note the tracheal deviation [2], although the lumen is free of tumor. Lymph node metastases are present. (Right) This lobe of the thyroid gland is greatly expanded by a multinodular and bosselated neoplasm. The tumor measures approximately 9 cm in greatest dimension.



Large, Multinodular Tumor

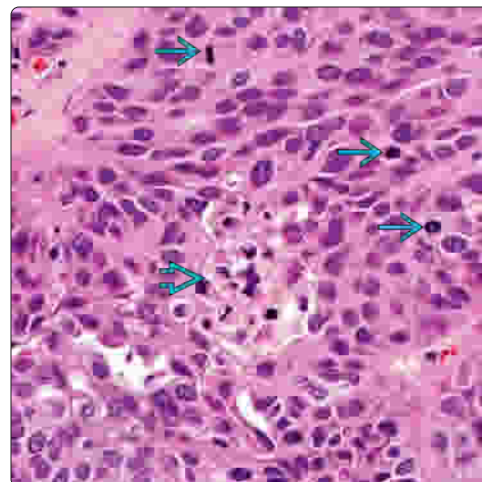


Fleshy, Widely Invasive Thyroid Tumor

(Left) The cut surface shows the thyroid parenchyma invaded by a neoplastic proliferation. The tumor is fleshy, with a yellow-tan appearance. Areas of degeneration and hemorrhage are noted. The tumor expands into the parenchyma and extends into the surrounding soft tissues. (Right) An epidermoid proliferation occupies this portion of an undifferentiated carcinoma. A central area of necrosis is noted [1]. Mitotic figures are easily identified [2].

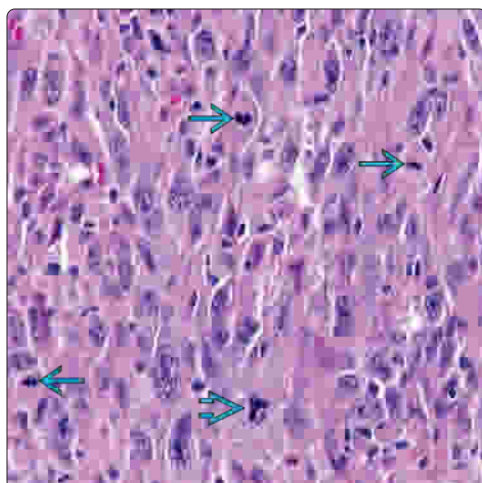


Tumor Necrosis Within Epidermoid Area

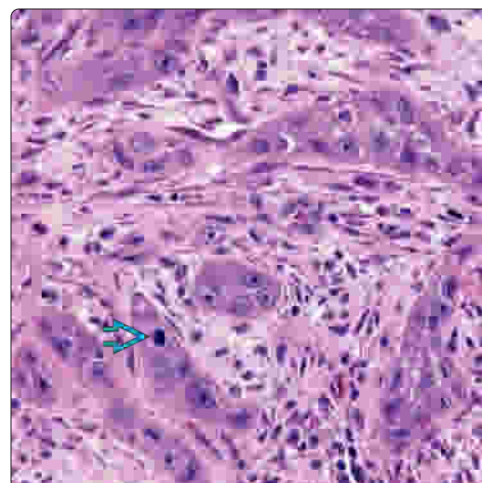


Spindled Neoplastic Cells

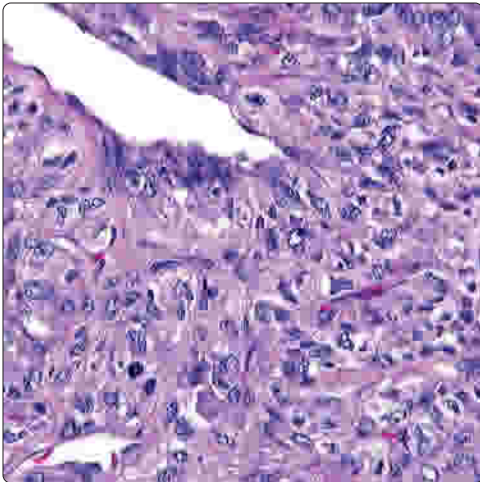
(Left) A fascicle comprised of spindled cells is noted in this undifferentiated carcinoma. There is significant pleomorphism as well as numerous mitotic figures [1], including atypical forms [2]. (Right) This epidermoid proliferation is intimately associated with a desmoplastic stroma. This is quite characteristic for this variant of undifferentiated carcinoma. Note the mitosis [1]. The cells are pleomorphic with prominent nucleoli.



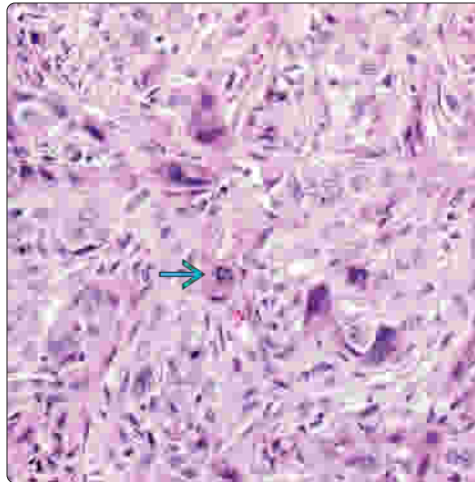
Cords of Pleomorphic Cells



Perivascular Growth

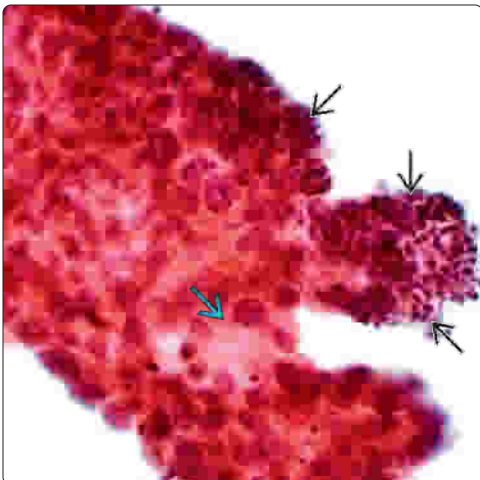


Pleomorphic Population With Mitoses

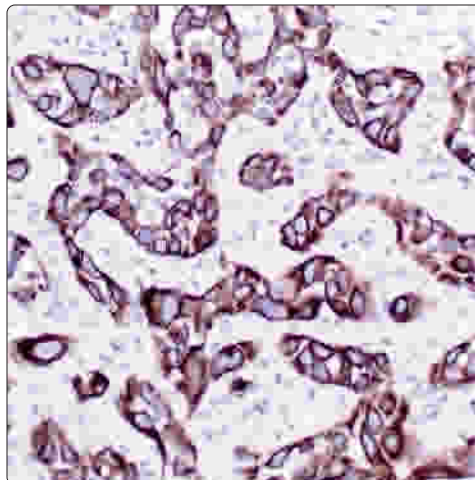


(Left) There is a highly pleomorphic population of neoplastic cells immediately adjacent to this vessel, suggesting an origin. However, the pattern can be seen in undifferentiated carcinoma and leiomyosarcoma. (Right) There is a highly atypical pleomorphic population of polygonal to spindled neoplastic cells in this undifferentiated carcinoma. Atypical mitoses are common.

Pleomorphic Epithelioid Cells With Inflammation

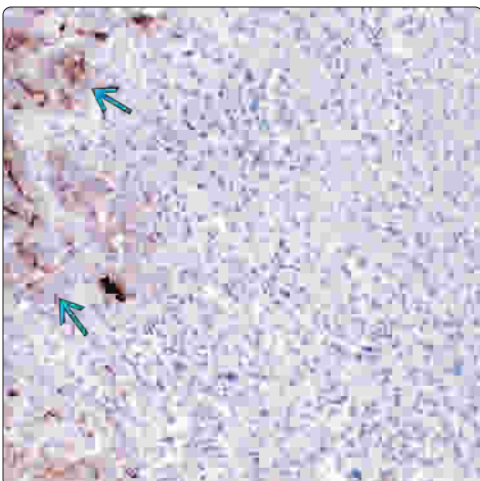


CK-PAN Highlights Polygonal Cells

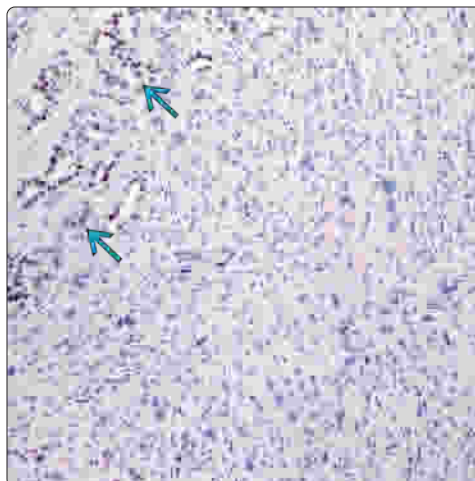


(Left) A fine-needle aspiration demonstrates a sheet of epithelioid cells, focally suggesting a "follicle". There are numerous acute inflammatory cells (neutrophils), a finding quite frequently seen in undifferentiated carcinoma. (Right) The neoplastic cells of the undifferentiated carcinoma are still positive with a pan-cytokeratin, helping to confirm the diagnosis of a carcinoma.

Thyroglobulin Negative in Tumor



TTF-1 Negative in Undifferentiated Carcinoma



(Left) A thyroglobulin is positive in the tall cell papillary carcinoma, while the pleomorphic and bizarre cells are not reactive. This is a characteristic finding with undifferentiated carcinoma. (Right) TTF-1 stains the nuclei of the residual papillary carcinoma, but the pleomorphic and bizarre cells are negative, a finding to be expected in undifferentiated carcinoma.

KEY FACTS

TERMINOLOGY

- Malignant C-cell-derived tumor with gain of function (activating) germline mutations of *RET* gene

ETIOLOGY/PATHOGENESIS

- Strong inherited association with MEN2A and 2B
- C-cell hyperplasia is precursor of medullary carcinoma
- Gain of function (activating) germline mutation of *RET* gene (usually point mutation) involving 10q11.2

CLINICAL ISSUES

- Sporadic: 5th to 6th decades; familial: 3rd decade
- Serum calcitonin and CEA levels elevated
- Cervical lymph node metastases: ~ 50%
- Total thyroidectomy (prophylactic for *RET* mutations), with neck dissection
- Overall 70-80% 10-year survival
- Tumor stage is most important prognostic factor (extrathyroidal extension; metastasis)

MICROSCOPIC

- Familial tumors are multifocal and bilateral
- Many patterns: Organoid, insular, solid sheets
 - Separated by heavily hyalinized fibrovascular stroma
- Amyloid stromal accumulation (70-80% of cases)
- Round, oval, spindled to plasmacytoid cells
- Stippled, fine, uniform nuclear chromatin
- Significant lymphovascular invasion

ANCILLARY TESTS

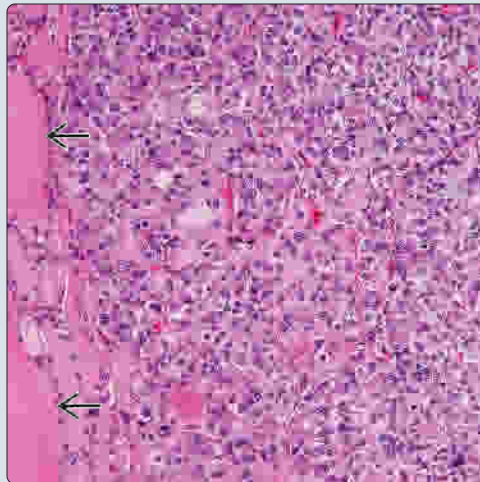
- Cellular aspirates with single cells and small, loosely cohesive clusters and extracellular amyloid spheres
- **Positive:** Calcitonin, chromogranin, synaptophysin, CEA-P, keratin, TTF-1

TOP DIFFERENTIAL DIAGNOSES

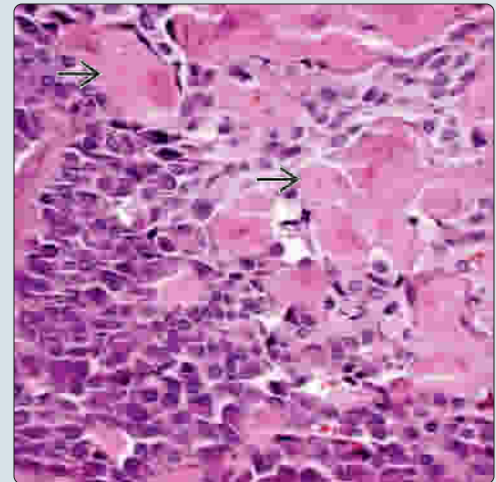
- Follicular carcinoma, papillary carcinoma, parathyroid adenoma, paraganglioma, undifferentiated carcinoma, metastatic carcinoma

Junction With Follicular Epithelium

(Left) There is a proliferation of epithelial cells arranged in sheets and nests. Note the intimate association with the thyroid follicles [E]. (Right) The cells of this medullary carcinoma are very plasmacytoid in appearance. The nuclei show delicate, salt and pepper nuclear chromatin distribution. Amyloid is quite prominent in this case [E].

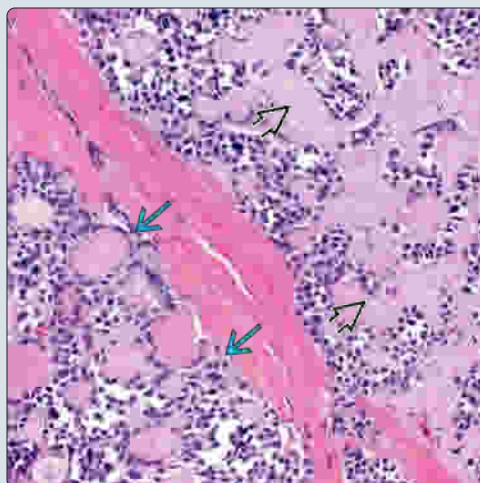


Plasmacytoid Cells With Amyloid



Junction With Thyroid Parenchyma

(Left) There is a junction between the medullary carcinoma [E] with associated amyloid and the thyroid follicular epithelium [E], separated by a dense fibrous connective tissue capsule. There is focal mingling. (Right) An aggregate of C cells forms a small nodule composed of > 50 cells. The surrounding thyroid follicles are not destroyed. There is no true fibrosis, no amyloid, and no cytologic atypia in this example of neoplastic C-cell hyperplasia.



Neoplastic C-Cell Hyperplasia



TERMINOLOGY

Abbreviations

- Medullary thyroid carcinoma (MTC)

Synonyms

- Solid carcinoma
- Solid carcinoma with amyloid stroma
- Solid amyloidotic carcinoma
- C-cell carcinoma
- Compact cell carcinoma
- Neuroendocrine carcinoma of thyroid

Definitions

- Malignant epithelial tumor of thyroid gland exhibiting C-cell differentiation

ETIOLOGY/PATHOGENESIS

Inherited

- Strong inherited association with multiple endocrine neoplasia (MEN) syndromes
 - MEN2A (Sipple): Parathyroid hyperplasia (hyperparathyroidism), thyroid medullary carcinoma, adrenal pheochromocytoma, pancreatic endocrine tumors
 - MEN2B (Wagenmann-Froboese syndrome): As above, with soft tissue tumors present (usually mucosal)
 - Autosomal dominant inheritance, high penetrance, and variable expressivity
 - Gain of function (activating) germline mutation of *RET* gene (usually point mutation) involving 10q11.2
 - Fusion gene with portion of gene coding for tyrosine kinase domain, called *RET* (**RE**arranged during **T**ransfection **C**ontraction)
 - *RET* receptor activates signaling pathways responsible for cell proliferation, survival, differentiation, motility, and chemotaxis
 - *RET* has 21 exons and ~ 55,000 base pairs, coding for RET protein, member of receptor tyrosine kinase superfamily
 - Mutations of extracellular 5 cysteine codons (exon 10: 609, 611, 618, 620; exon 11: 634) collectively account for ~ 95% of MEN2A and 85% of FMTC kindred
 - Specifically, codon 634 is involved in 80-90% of MEN2A cases (arginine for cysteine substitution most commonly)
 - ~ 95% of MEN2B associated with point mutation in codon 918 of exon 16 (Met918Thr substitution)
 - *RET* also involved in thyroid papillary carcinoma (chromosomal rearrangement known as *RET/PTC*)
- Familial medullary thyroid carcinoma (FMTC) can be seen **without** extrathyroid associations but still with germline mutation in *RET* proto-oncogene

Sporadic

- Up to 2/3 of sporadic medullary carcinomas have somatic *RET* mutations
- Other genetic &/or epigenetic alterations are involved
- Genetic variants of sporadic form are still poorly understood

Pathogenesis

- Ultimobranchial body gives rise to C cells, which are source of tumor development
 - C cells (parafollicular cells) arise embryologically from 4th branchial/pharyngeal pouch
 - Found in upper and middle regions of thyroid gland lobes
 - Medullary carcinoma does not arise from isthmus
 - Calcitonin, hormone involved in calcium homeostasis, is peptide secreted by C cells
 - Calcitonin gene-related peptide (CGRP) tends to be seen in extrathyroidal sites
- C-cell hyperplasia is precursor of medullary carcinoma in heritable cases

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~ 5-8% of all thyroid malignancies in USA
 - Majority are sporadic (80%), with remaining (20%) inherited (familial)
- Age
 - Sporadic: 5th-6th decades
 - Familial: 3rd decade
 - MEN2A: Late adolescence or early adulthood
 - MEN2B: Infant to early childhood
- Sex
 - Female > male (1.1:1) for sporadic cases

Site

- Middle to upper part of thyroid lobes
 - Usual location for C cells &/or ultimobranchial body
- Isthmus **not** affected

Presentation

- Sporadic
 - Painless, unilateral, solitary thyroid mass
 - Cervical lymph node enlargement in about 50%
 - Hoarseness, stridor, upper airway obstruction, or dysphagia in ~ 10-15%
- Inherited/familial
 - Similar thyroid/neck findings, although usually at younger age
 - Diarrhea and flushing (up to 30% of patients) related to high plasma calcitonin levels
 - Multicentric and bilateral thyroid involvement
 - Nonthyroid symptoms related to other organ disorders may dominate clinical presentation
 - Hyperparathyroidism with calcium homeostasis derangements
 - Sweating, headache, paroxysmal hypertension, palpitations, syncope, and dizziness related to pheochromocytoma
 - Cushing syndrome due to tumor ACTH production or part of pituitary adenoma peptide production
 - Gastrointestinal symptoms related to pancreatic endocrine tumor peptide secretion
 - Mucosal neuromas (oral cavity, lips, tongue, and gastrointestinal tract)

- If part of kindred, early detection before clinical symptoms present
 - Parathyroid, adrenal, pituitary, pancreas, and gastrointestinal tract findings
 - Thyroid disease discovered incidentally during evaluation of MEN syndrome

Laboratory Tests

- Serum calcitonin levels are almost invariably increased
- CEA level elevated
- Calcium imbalances (due to calcitonin &/or parathyroid hormone abnormalities)

Treatment

- Options, risks, complications
 - Prophylactic thyroidectomy for patients with germline *RET* mutations (*RET* genotype specific)
 - Specific *RET* codon mutation will dictate recommended age at thyroidectomy
 - Codon 883, 918, & 922 mutations: Thyroidectomy before 12 months of age
 - Codon 611, 618, 620, & 634 mutations: Thyroidectomy before 5 years of age
 - Other codons: Thyroidectomy, usually after pentagastrin-stimulated calcitonin response becomes abnormal
 - Serum calcitonin and CEA levels before surgery as tumor marker and prognostic factor (used for subsequent monitoring)
 - Serum calcium, urinary metanephrine, and catecholamines to exclude MEN-associated diseases
- Surgical approaches
 - Total thyroidectomy
 - Neck dissection
 - Central compartment (level VI)
 - If central lymph nodes positive or tumor > 1 cm, ipsilateral neck dissection
 - If bilateral tumors, bilateral radical neck dissections are recommended
 - Parathyroidectomy if part of heritable disease
- Adjuvant therapy
 - Chemotherapy, somatostatin analogs, anti-CEA radioimmunotherapy is employed in some
- Drugs
 - Various drugs, such as Vandetanib (oral tyrosine kinase inhibitor targeting *RET* kinase) are used for symptomatic, progressive, metastatic MTCs
- Radiation
 - External beam radiation for gross residual disease or palliation of distant metastases
 - ¹³¹I-metaiodobenzylguanidine (MIBG) radiation (radiolabelled) reduces tumor volume
 - Radiofrequency ablation

Prognosis

- Clinical stage and inherited-type dependent
 - Overall ~ 70–80% 10-year survival
 - Excellent prognosis for small tumors confined to thyroid, incidentally discovered and without lymph node metastases (100%)
 - Survival outcomes: Familial non-MEN > sporadic > MEN2A > MEN2B

- Prophylactic thyroidectomy patients have best prognosis (naturally) and least likely to have lymph node metastases
- Tumor stage is most important prognostic factor (extrathyroidal extension; metastasis)
 - Stage I: 100% 10-year survival
 - Stage III: 65-85% 10-year survival
 - Stage IV: 20-50% 10-year survival
- Young patients (< 45 years) have better prognosis than older patients
- Males may have slightly worse outcome (controversial)
- Lymph node metastases common (50% at presentation)
- Distant metastases uncommon (15% at presentation)
 - Liver, lungs, bone
- Better prognosis for tumors with abundant amyloid and > 75% calcitonin-positive cells
- If somatic *RET* mutation is present, those with codon 918 mutation appear to be more aggressive
- If preoperative serum calcitonin &/or CEA levels were elevated, they can be followed to monitor disease status
- Genetic screening (biochemical or molecular) recommended for relatives of proband (found in 10-15% of cases)

IMAGING

General Features

- ¹³¹I-MIBG positive mass
 - Radiopharmaceutical and guanethidine analog confirms neuroendocrine nature of tumor
- 6-fluoro-([¹⁸F]-L-3,4-dihydroxyphenylalanine (FDOPA) is amino acid analogue for positron emission tomography (PET) imaging
 - Detects recurrent MTC in ~ 70% of patients
- Cold mass on scintigraphic scan
- Computed tomography (CT) shows extent of disease and lymph node status
- PET can be used to identify distant metastases
- Ultrasound shows mass lesion

MACROSCOPIC

General Features

- Sporadic tumors are unilateral and solitary
- Familial tumors are multifocal and bilateral
- Usually well-defined, but poorly formed capsule, with infiltration
- Involve middle to upper, lateral portion of lobe(s)
- Tan-yellow, white to light gray
- Firm, rubbery cut surface; rarely soft consistency
- Gritty due to finely granular calcifications
- Hemorrhage or necrosis usually absent

Sections to Be Submitted

- If prophylactic thyroidectomy, lobes should be serially sectioned transversely and sections submitted sequentially from superior to inferior
 - Calcitonin may be necessary to highlight areas of C-cell hyperplasia or microcarcinoma

Size

- Microscopic up to 10 cm

- Large tumors may completely replace lobe

MICROSCOPIC

Histologic Features

- Broad range of histologic features
- Multitude of growth patterns
 - Solid sheets and nests, separated by heavily hyalinized fibrovascular stroma
 - Lobular, organoid, nested, insular, and trabecular tend to be more defined by stroma
 - Curvilinear anastomosing cells separated by delicate and thin, to more thick and hyalinized, stroma of tumor
- Amyloid stromal accumulation (70-80% of cases)
 - Homogeneous, acellular, eosinophilic, extracellular matrix material
 - Appears to be calcitonin-derived
 - May be associated with calcification
 - Calcifications may resemble psammoma bodies but without concentric laminations
 - Tumors lacking amyloid tend to have worse prognosis
- Entrapment of benign follicular epithelial cells is common
 - Can extend quite deeply into main tumor mass
- Cells are round to oval, spindled to plasmacytoid or polyhedral cells
 - Mixtures of these cell types are common
- Nuclei are round to oval nuclei with stippled, fine, uniform salt and pepper nuclear chromatin
 - Nucleoli are only prominent in oncocytic variant
- Intranuclear cytoplasmic inclusions common
- Cells have mild to moderate pleomorphism, although isolated bizarre nuclei are common
 - Bi- and multinucleated cells can be seen
- Cytoplasm is opaque, finely granular, and ranges from eosinophilic to clear, amphophilic, oncocytic, and pigmented
 - Intracytoplasmic mucinous vacuoles with extracellular mucin accumulation can be seen
- Mitotic figures are infrequent
- Necrosis is uncommon, possibly seen in large tumors
- Significant lymphovascular invasion
- Extensive invasion of tumor capsule, with expansion into thyroid parenchyma and extrathyroidal soft tissues
- Metastatic deposits in lymph nodes
 - Particularly central paratracheal or superior mediastinum

Precursor

- Solid cell nests are thought to be remnants of ultimobranchial body
 - Nests of paved cells without intercellular bridges
 - Usually seen in and around areas of C-cell proliferation
- C-cell hyperplasia: Reactive or neoplastic
- **Reactive (secondary; physiologic)**
 - Reactive increase seen in thyroids removed for other disorders (nodules, lymphocytic thyroiditis, papillary and follicular carcinoma)
- **No** aggregates of > 50 cells; **no** destructive growth; **no** amyloid deposition; **no** fibrosis; **no** cellular pleomorphism

- Frequently seen adjacent to solid cell nests (ultimobranchial body remnant)
- Usually requires calcitonin &/or chromogranin to highlight

Neoplastic

- Also called C-cell carcinoma in situ or medullary carcinoma in situ
- Seen adjacent to medullary carcinoma and in asymptomatic carriers of *RET* germline mutations
- May be focal, diffuse, or nodular
- Groups of C cells surrounding or partially destroying follicles
- Aggregates of > 50 cells
- May be associated with amyloid deposition and fibrosis
- Separation from "microcarcinoma" or intraglandular spread from medullary carcinoma may be challenging

Variants

- Oncocytic cell, papillary/pseudopapillary, glandular or follicular, giant cell, small cell, paraganglioma-like, spindle cell, clear cell, squamous cell, melanin-producing, angiosarcoma-like, amphi-ricine
- Each of these patterns mimics other primary or secondary tumors
- Immunohistochemical confirmation usually required

ANCILLARY TESTS

Cytology

- Frequently challenging due to wide cytologic variability
- Cellular aspirates with single cells and small, loosely cohesive clusters
- Extracellular, homogeneous, amorphous eosinophilic clumps or spheres of amyloid (up to 70% of aspirates)
 - Dark blue-purple on air-dried Diff-Quik slides and opaque, deep green on Papanicolaou-stained slides
- Colloid absent
- Round to oval, spindle, bipolar to polygonal cells
- Rare cells with moderate pleomorphism
- Scattered bi- and multinucleated cells
- Plasmacytoid appearance with eccentric nucleus placement (plasmacytoid)
- Hyperchromatic nuclei with stippled to coarse nuclear chromatin (salt and pepper)
- Intranuclear cytoplasmic inclusions frequent
- Abundant, eosinophilic cytoplasm
- Metachromatic red cytoplasmic granules on air-dried preparations
- Calcitonin immunostain may be helpful

Histochemistry

- Grimelius stain highlights argyrophilic granules
 - Negative with Fontana-Masson stain
- Intra- &/or extracellular mucin
 - Highlighted with mucicarmine, Alcian blue, &/or PAS
- Congo red positive in amyloid
 - Light green birefringence with polarization
- Crystal violet positive in amyloid
 - Purple metachromatic staining

Immunohistochemistry

- **Positive:** Calcitonin, chromogranin, synaptophysin, CEA-P, keratin, TTF-1
- **Negative:** Thyroglobulin

Flow Cytometry

- ~ 30% are aneuploid (possibly associated with worse prognosis)

Genetic Testing

- Germline or somatic *RET* mutations
- Can be performed on peripheral blood
 - Exons 10, 11, 13, 14, 15, and 16 of *RET* are typically analyzed
 - Restriction fragment length polymorphism assays, single-strand conformation polymorphism, heteroduplex techniques, or DNA sequencing

Electron Microscopy

- Neurosecretory electron dense membrane bound granules (type I and II) help to confirm neuroendocrine nature of medullary carcinoma
- Extracellular spaces contain finely fibrillar amyloid material

DIFFERENTIAL DIAGNOSIS

Follicular Carcinoma

- Trabecular and oncocytic patterns cause most quandary
- Colloid is usually difficult to detect, but nuclei tend to be more hyperchromatic
- Thyroglobulin is positive
 - Calcitonin negative (sensitive and specific)

Papillary Carcinoma

- Nuclear features of papillary carcinoma are usually not seen in medullary carcinoma
- Intranuclear inclusions seen in both tumors
- Immunohistochemistry profile is different

Parathyroid Tissue

- Parathyroid tissue (normal glands or neoplasms) usually shows cleared cytoplasm, well-defined cell borders
- Parathyroid hormone positive, lacking calcitonin and thyroglobulin

Paraganglioma

- Well-defined tumor, lacking invasion
- Zellballen architecture with S100 protein (+) sustentacular cells
- Negative for calcitonin and thyroglobulin

Undifferentiated (Anaplastic) Carcinoma

- Usually older age, rapid onset of tumor
- Spindle cell pattern with pleomorphism can be difficult
- Increased mitotic figures, necrosis, hemorrhage, and association with existing thyroid lesion
- Calcitonin should help

Metastatic Carcinoma

- **Renal cell carcinoma**
 - Solitary mass but often with lymphovascular invasion
 - Tumor cells are clear with pseudoglandular erythrocyte collections

- Thyroglobulin, calcitonin, CD10 may help with separation, as only latter is positive

Metastatic melanoma

- If melanin pigment is present, differential is raised
- Melan-A, HMB-45, and tyrosinase can help (not S100 protein)

Metastatic neuroendocrine tumors

- Quite uncommon
- Includes carcinoid, atypical carcinoid, and neuroendocrine carcinomas
- All are typically negative for calcitonin and CEA, but require clinical, radiological, laboratory integration
- Direct extension from larynx must be excluded, as calcitonin can be positive

C-Cell Hyperplasia vs. Intraglandular Spread

- Multifocal; aggregates of cells, often adjacent to ultimobranchial body
- Usually lacking destructive growth
- Not within lymphovascular spaces
- Associated with possible fibrosis
- Tends to show increased calcitonin intensity over medullary carcinoma

Hyalinizing Trabecular Tumor

- Encapsulated tumor without invasion
- Trabecular growth pattern
- Intralesional hyalinization without amyloid
- Cells are spindled, arranged perpendicular to stroma
- Yellow intracytoplasmic bodies
- Thyroglobulin (+), calcitonin (-)

Amyloid Goiter

- Unencapsulated, affecting whole gland
- Fatty infiltration with squamous metaplasia and amyloid deposition (Congo red positive)

Lymphoma

- Diffuse, unencapsulated lesion
- Background of chronic lymphocytic thyroiditis (rare in medullary carcinoma)
- Spectrum of lymphoid elements (plasmacytoid cells with Dutcher bodies; immunoblasts, centrocytes, monocytoid B cells)
- Hematologic immunohistochemistry (CD20, CD19, CD79a, CD138, κ , λ)

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Must consider medullary in any tumor that is slightly atypical
- Oncocytic tumors without colloid production, must have PAS or thyroglobulin performed to confirm cell type

STAGING

Distribution

- Stage I: 20%
- Stage II: 33%
- Stage III: 32%
- Stage IV: 15%

Immunohistochemistry

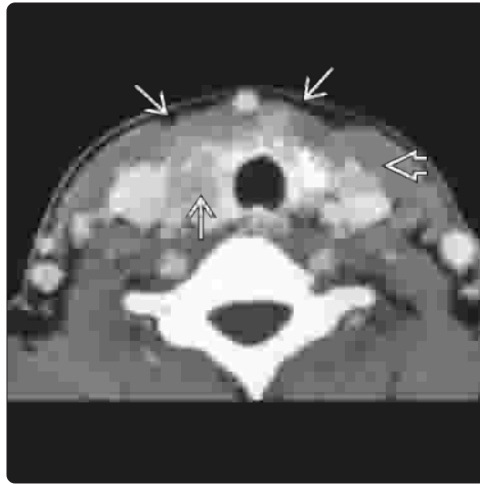
Antibody	Reactivity	Staining Pattern	Comment
Calcitonin	Positive	Cytoplasmic	Strong, diffuse, and most specific marker, present in ~ 95% of cases
CGRP	Positive	Cytoplasmic	May be limited to small foci within tumor
CEA-P	Positive	Cytoplasmic	Usually immunoreactive in most tumor cells, even more commonly than calcitonin
TTF-1	Positive	Nuclear	Variable intensity, slightly less than follicular tumors
Chromogranin-A	Positive	Cytoplasmic	Granular reactivity
Chromogranin-B	Positive	Cytoplasmic	Granular reactivity
Synaptophysin	Positive	Cytoplasmic	Granular to dot-like
NSE	Positive	Cytoplasmic	Most tumor cells positive but usually not helpful in diagnosis
Serotonin	Positive	Cytoplasmic	Frequently positive
Somatostatin	Positive	Cytoplasmic	Occasionally reactive
AE1/AE3	Positive	Cytoplasmic	Strong and diffusely positive
CK7	Positive	Cytoplasmic	Strong and diffuse, slightly more membrane than pankeratin
Vimentin	Positive	Cytoplasmic	Variably positive in tumor cells
S100	Positive	Nuclear & cytoplasmic	Often in sustentacular distribution around nests
Calretinin	Positive	Nuclear & cytoplasmic	Only in about 25% of tumor cells
Galectin-3	Positive	Cytoplasmic	Variably present (45-80%) but weak and focal to strong
Thyroglobulin	Negative		
CK20	Negative		

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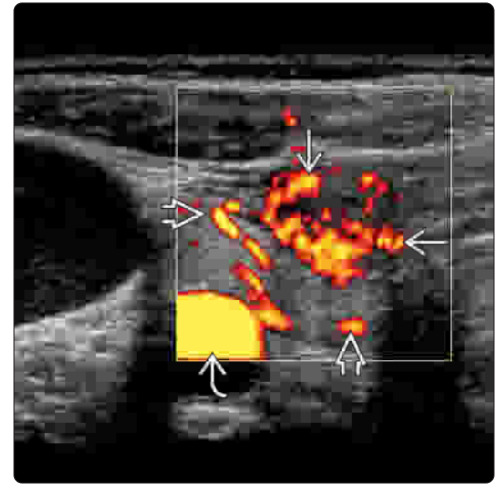
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CT of Thyroid Gland With Lymph Node Metastases

(Left) Axial post-contrast CT through the neck shows marked irregularity of the thyroid gland with multiple focal areas of decreased intensity. The borders of the gland are ill-defined. There is an adjacent, abnormally enlarged left lymph node indicating metastatic disease. (Right) Transverse power Doppler ultrasound shows chaotic intralobular flow as compared to the normal thyroid gland. Note the internal carotid artery as a point of comparison. (Courtesy A. Ahuja, MD.)

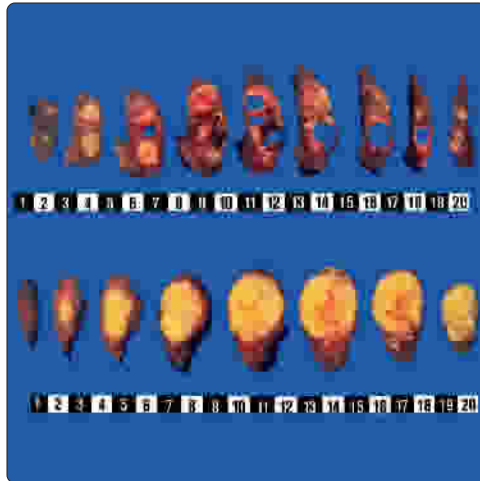


Ultrasound With Chaotic Flow

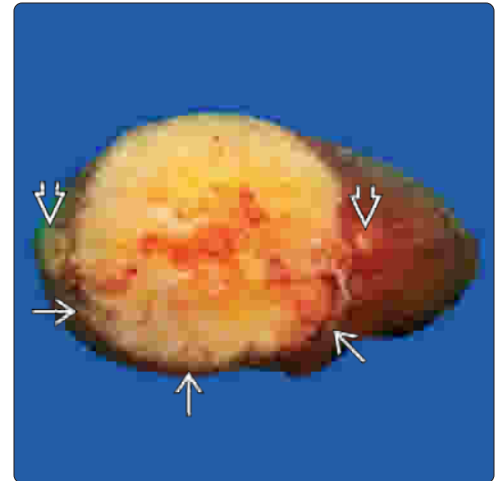


Bilateral Medullary Carcinoma Gross Photo

(Left) Serial sections of both lobes of the thyroid gland show tumors. This is an example of familial medullary carcinoma, showing bilateral and multifocal tumors. Note the areas of cystic change in the upper series. (Right) There is a large tumor, measuring approximately 3.8 cm, shown here. The edge is infiltrative, although a well-formed capsule is not present. Smaller tumor nodules are noted adjacent to the main mass.

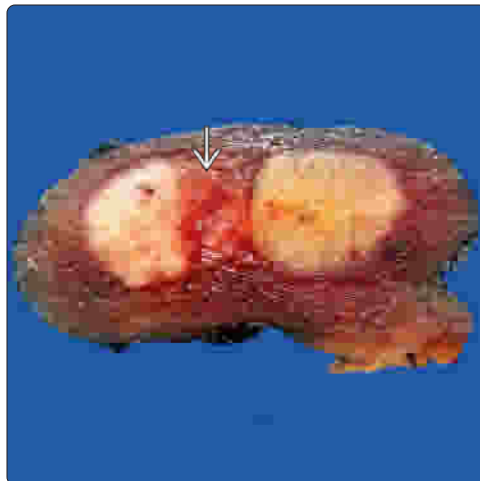


Infiltrative Medullary Carcinoma Gross Photo

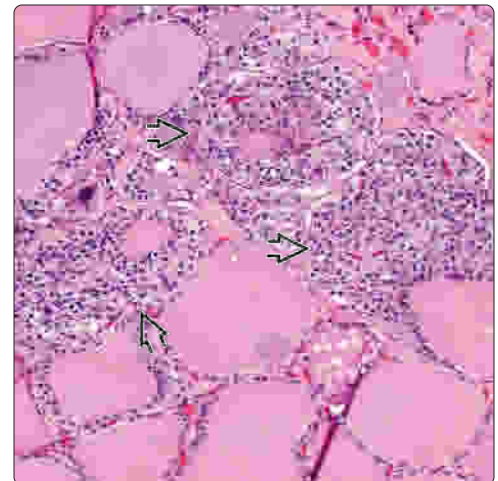


Multifocal Tumors in Inherited Syndrome Gross Photo

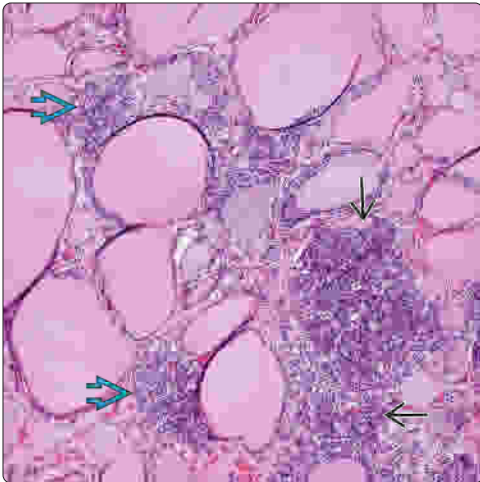
(Left) This lobe demonstrates multifocal disease within a single lobe. The tumors are topographically separate and show different cut appearances. Multifocal disease is characteristic for inherited/familial tumors. One tumor shows an area of cystic change. (Right) There are several collections of > 50 cells in this field, intimately associated with the thyroid follicular epithelium. There is no destructive growth, no fibrosis, and no amyloid. This is an example of neoplastic C-cell hyperplasia.



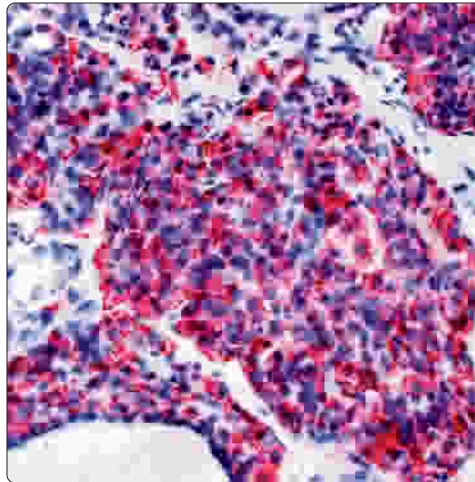
Neoplastic C-Cell Hyperplasia



Microscopic Medullary Carcinoma With C-Cell Hyperplasia

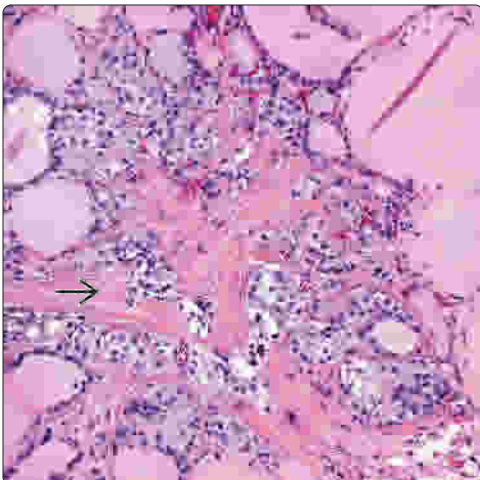


Calcitonin Reaction for Neoplastic C-Cell Hyperplasia

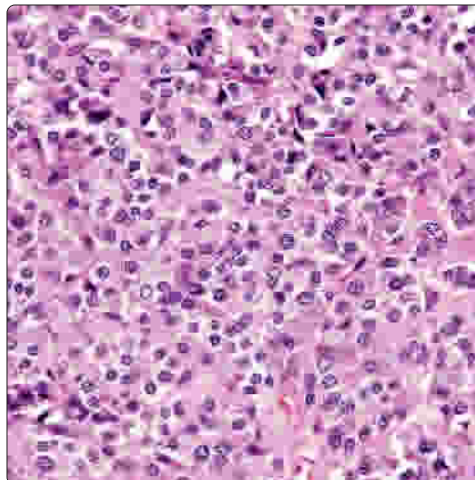


(Left) There is a microscopic medullary carcinoma noted in the background of the neoplastic C-cell hyperplasia that is seen here. This is often seen in syndrome-associated cases. (Right) The C-cells are strongly and diffusely reactive with calcitonin in this example of neoplastic C-cell hyperplasia. It shows a nondestructive growth and lacks fibrosis and amyloid.

Microscopic Medullary Carcinoma

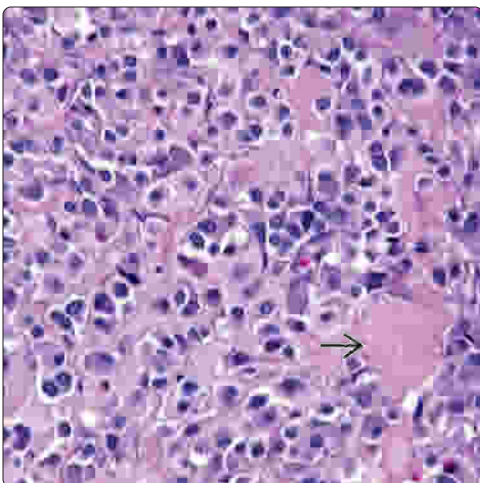


Nested Arrangement

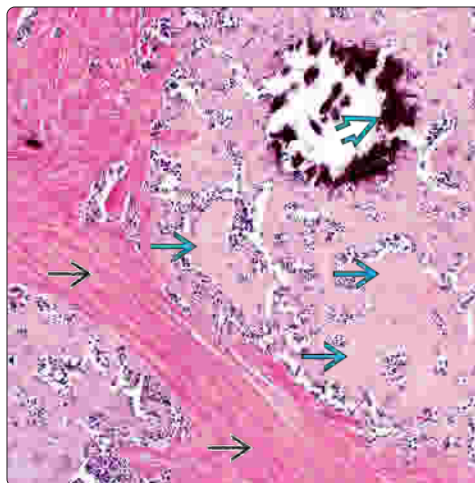


(Left) There is a stellate fibrosis associated with an infiltrative C-cell proliferation this is seen here. The neoplastic cells are arranged in small groups. Amyloid is not seen. (Right) There is a vague nesting in this sheet of neoplastic cells. Note the granular, slightly basophilic cytoplasm surrounding nuclei that have delicate chromatin distribution.

Organoid Architecture



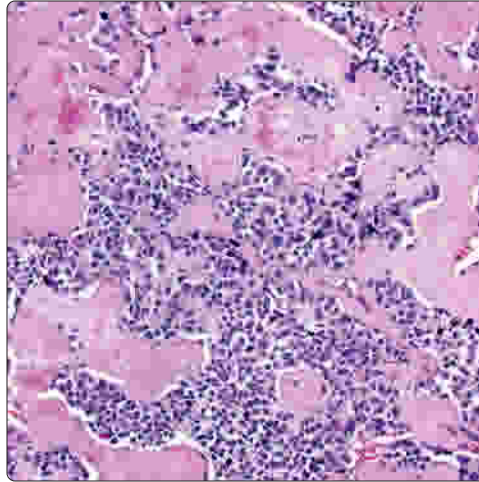
Fibrosis and Amyloid in Medullary Carcinoma



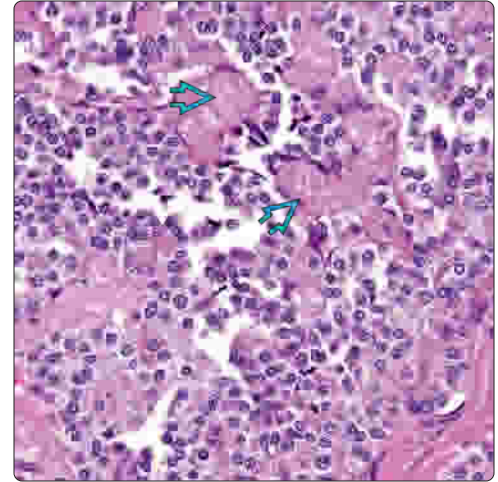
(Left) There is a sheet-like to organoid architecture to this medullary carcinoma. The cells have slightly bluish-granular cytoplasm. There is a plasmacytoid appearance to the cells. Amyloid is noted. (Right) As seen here, there are heavy bands of fibrosis (brightly eosinophilic) that are separating the tumor into nodules. There is abundant amyloid: Acellular, opaque, eosinophilic, extracellular matrix material. Calcification is also present within the amyloid.

Amyloid Blending With Tumor Cells

(Left) There is a blending of the epithelial cells of this medullary carcinoma with the acellular, eosinophilic amyloid. (Right) There is a solid architecture, showing focal degenerative changes, in this medullary carcinoma. Note the small concretions of amyloid.

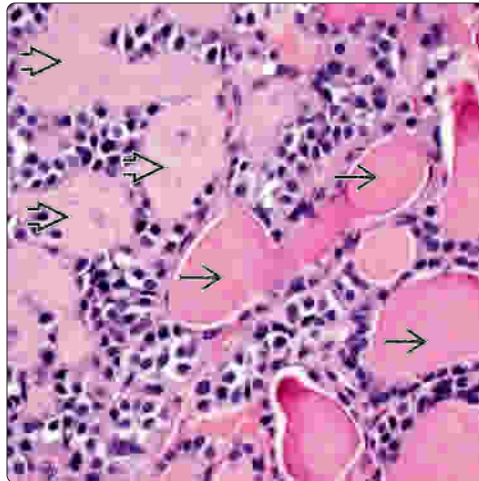


Solid Architecture

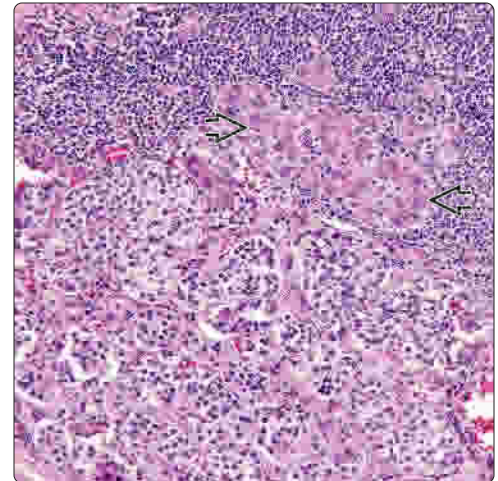


Carcinoma Infiltrating Thyroid Follicles

(Left) The distinction between entrapped follicular epithelium with colloid and amyloid can sometimes be a challenge. The tinctorial quality differences, along with the chatter artifacts in the colloid help. (Right) There is an infiltrative nested appearance to the medullary carcinoma as it infiltrates into thyroid parenchyma affected by chronic lymphocytic thyroiditis. Note the oncocytic metaplasia of the follicular epithelium within the lymphocytic thyroiditis.

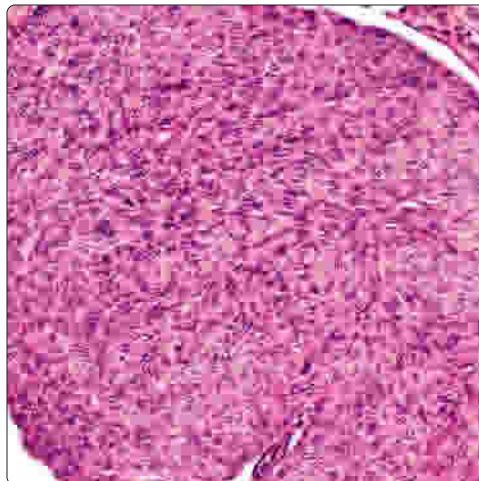


Medullary Carcinoma and Lymphocytic Thyroiditis

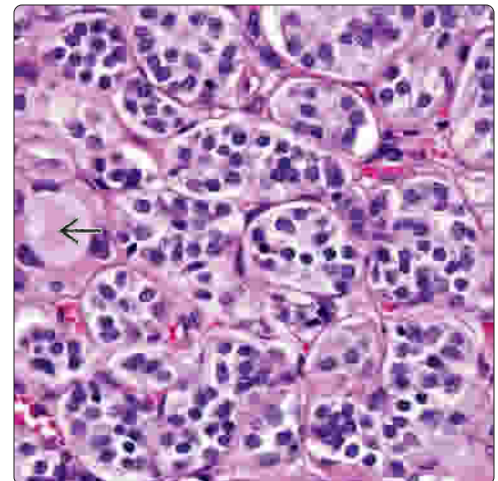


Solid Pattern of Medullary Carcinoma

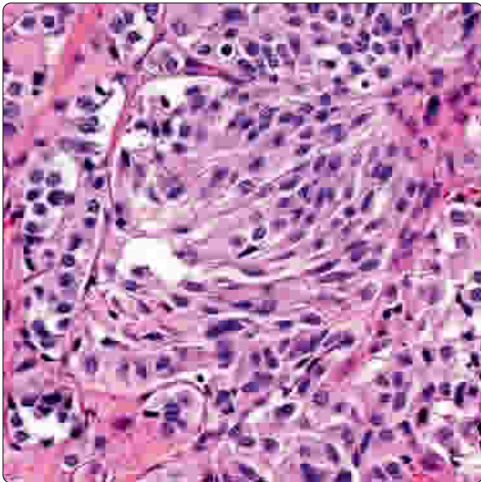
(Left) A solid pattern is shown, composed of cells that have a spindled appearance. The nuclei seem to have an optical clearing. This was not the dominant finding in this medullary carcinoma but was a focal pattern, seen in < 20% of the tumor. (Right) A characteristic nested pattern with cells that have small round nuclei and granular cytoplasm is seen in this medullary thyroid carcinoma. Note the entrapped colloid at the periphery. This should not be misinterpreted as follicular differentiation.



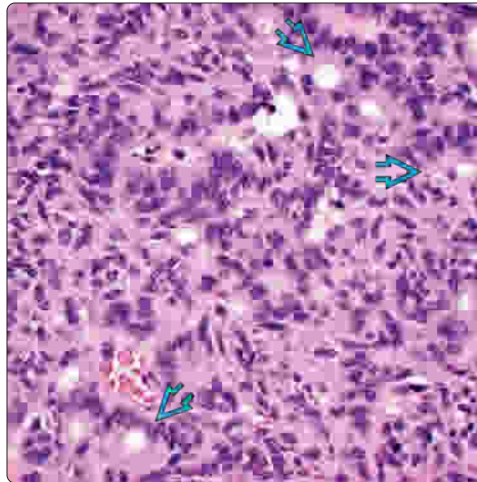
Nested Pattern in Medullary Carcinoma



Spindled Pattern in Medullary Carcinoma

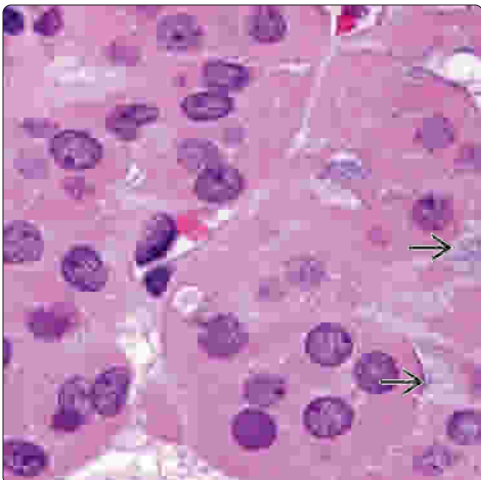


Mixed Patterns in Medullary Carcinoma

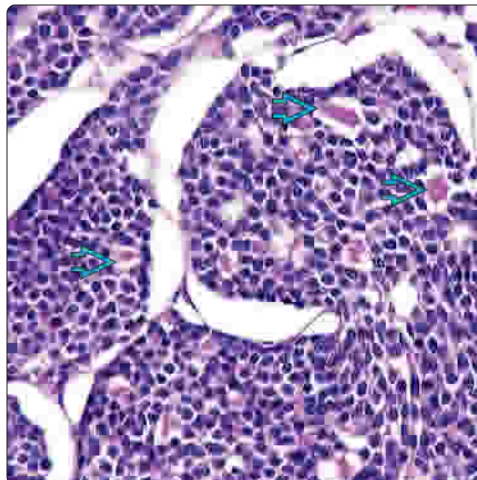


(Left) A spindled cell appearance is frequently seen in medullary carcinoma, although it is uncommon as a dominant pattern. There is a syncytial appearance. The nuclei are spindled to oval with delicate nuclear chromatin distribution. (Right) There is a mixed glandular, insular, and spindled cell appearance to this medullary carcinoma. There is a rosette-type pattern, lacking secretions.

Oncocytic Variant in Medullary Carcinoma

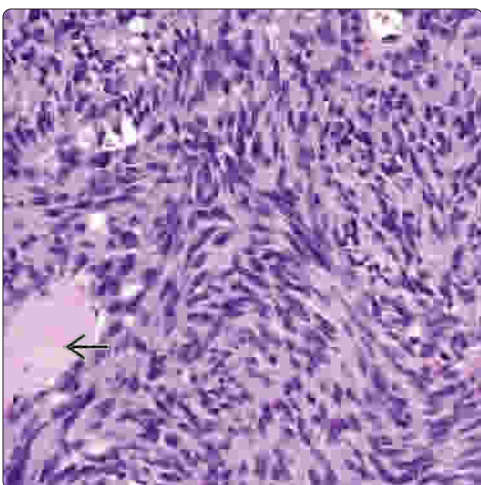


Glandular Pattern in Medullary Carcinoma

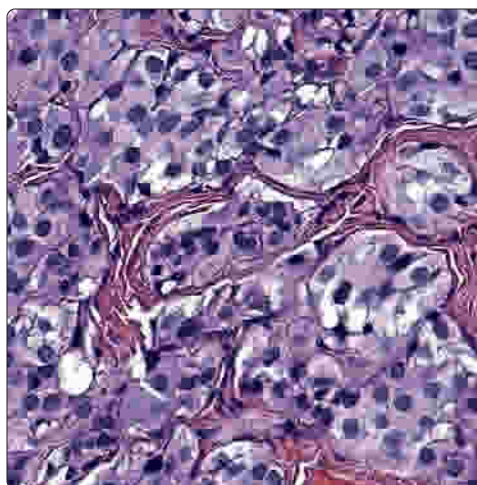


(Left) Oncocytic variant is quite difficult to diagnose. There are small but prominent nucleoli. Note the mucinous material within the cytoplasm or between a few of the cells. Immunohistochemistry is useful in these cases to help confirm the C-cell derivation. (Right) This tumor is arranged in a sheet-like and glandular architecture. The cells are syncytial, with a high nuclear to cytoplasmic ratio. Glandular lumen with secretions are noted, a pattern seen in many medullary carcinomas.

Fascicular Pattern of Spindled Cells



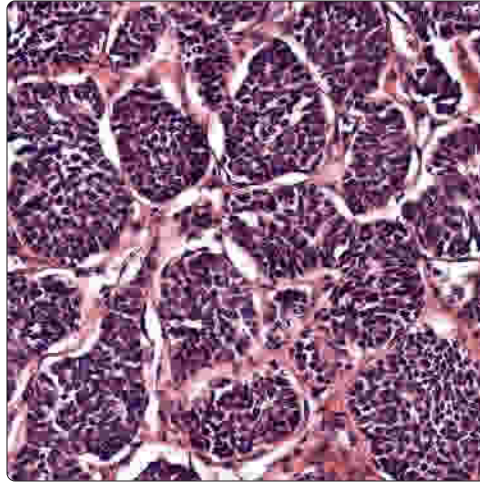
Alveolar Pattern in Medullary Carcinoma



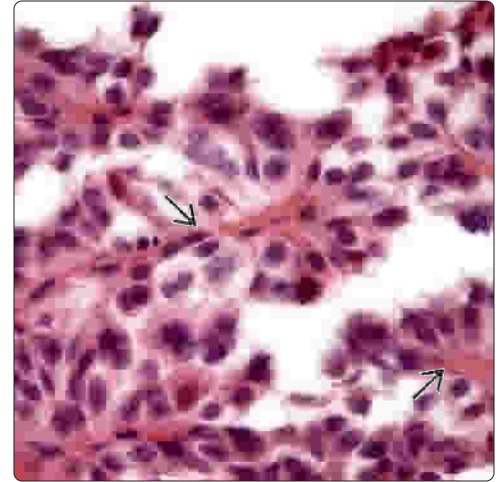
(Left) There is a fascicular architecture comprised of spindled cells in this medullary carcinoma. A small focus of amyloid is noted. (Right) A zellballen-type appearance can sometimes be seen in medullary carcinoma. The cytoplasm is granular to basophilic, a helpful feature in confirming the diagnosis. There is a delicate fibrous stroma surrounding the tumor cell nests.

Insular Pattern in Medullary Carcinoma

(Left) The insular or organoid architecture is one of the more characteristic appearances for medullary carcinoma. Note the delicate fibrovascular septations that surround the tumor nests. **(Right)** A papillary to pseudopapillary appearance can be seen in medullary carcinoma. There is a delicate fibrovascular core [E], covered with the neoplastic cells. However, the spaces between the papillary fronds suggests a background of degeneration.

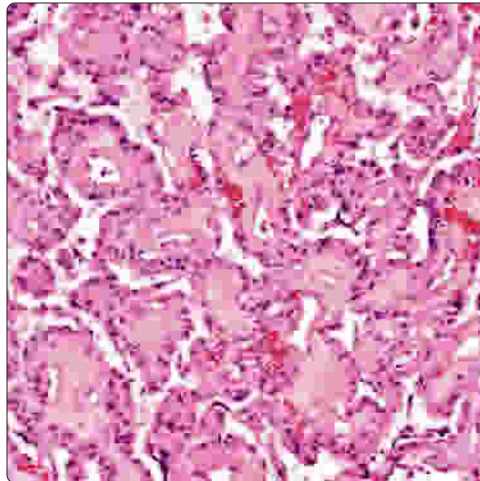


Papillary Pattern in Medullary Carcinoma

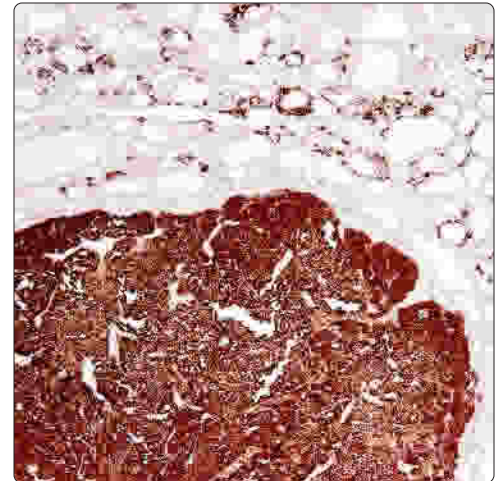


Angiomatoid Pattern in Medullary Carcinoma

(Left) An angiomatoid or vascular pattern, mimicking an angiosarcoma, is seen in this medullary carcinoma. In general, the variant histology should be the dominant finding. Special studies usually help to confirm the diagnosis. **(Right)** Calcitonin is one of the most specific stains for medullary carcinoma. Note the strong and heavy deposition of chromogen within the tumor, but there is also a background of C-cell hyperplasia in the surrounding parenchyma, highlighted by the calcitonin immunohistochemistry.

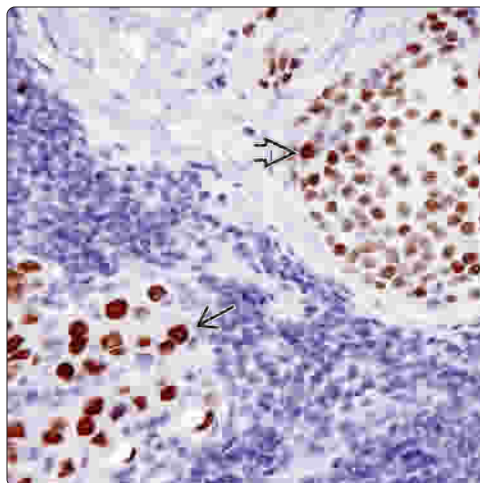


Calcitonin Immunoreactivity

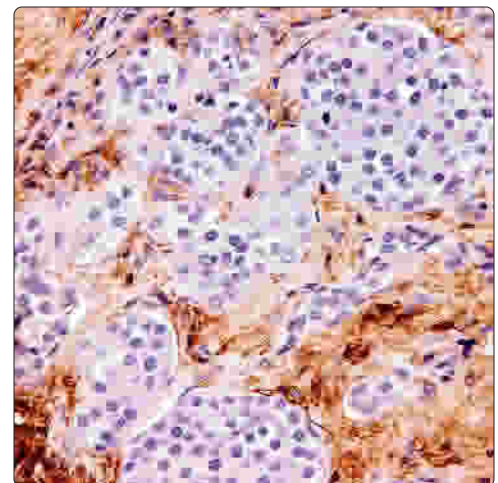


TTF-1 Immunoreactivity

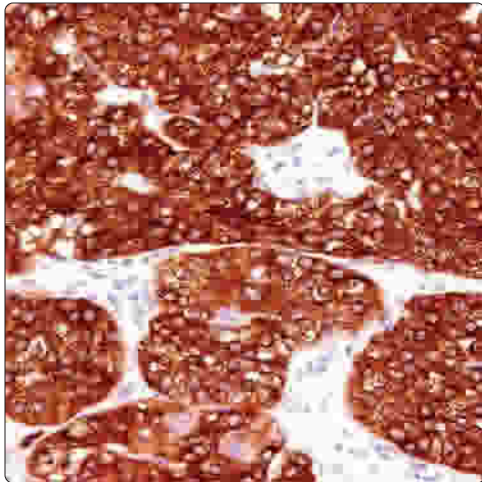
(Left) The medullary carcinoma cells seen here are strongly positive [E], but so is the uninvolved thyroid gland parenchyma [E]. This study only confirms thyroid origin and is not helpful in confirming medullary carcinoma. **(Right)** Thyroglobulin can be difficult to interpret, as there are diffusion artifacts and background reactivity from the plasma/serum. The neoplastic cells are negative in this medullary carcinoma.



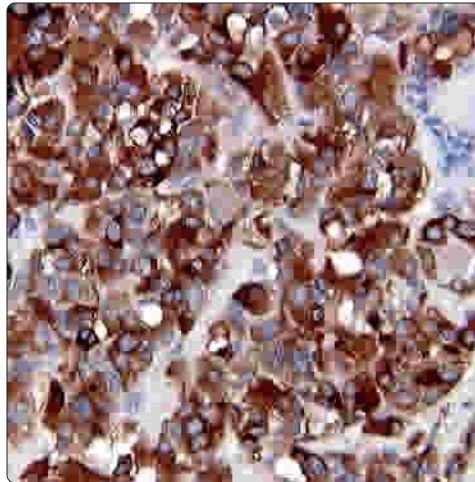
Thyroglobulin in Medullary Carcinoma



CEA-P in Medullary Carcinoma

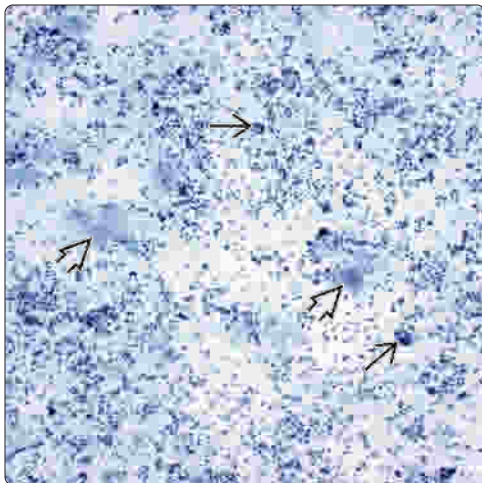


Chromogranin Reaction in Medullary Carcinoma

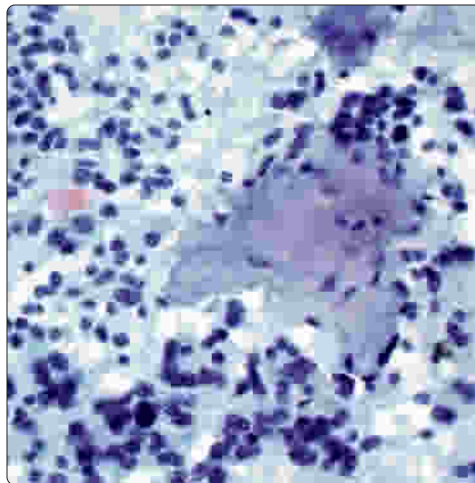


(Left) CEA usually gives a strong, heavy, cytoplasmic granular reactivity in medullary carcinoma. Polyclonal CEA is preferred to monoclonal, as there is a greater degree of sensitivity. (Right) There is a variable granular positive reaction with chromogranin that is seen here. Note how some of the cells are strongly and diffusely immunoreactive, while other cells show less staining, with a weaker reaction.

Cellular Smear

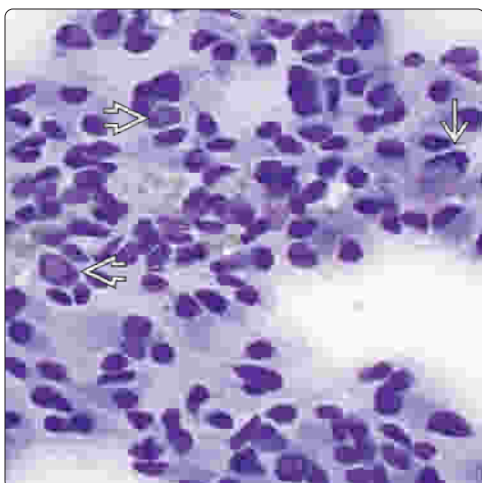


Amyloid in FNA Smear

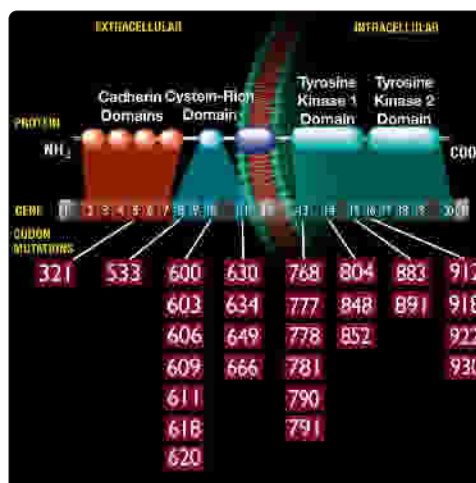


(Left) The smears seen here are cellular, showing small groups and single cells in a medullary carcinoma. Amyloid is easily identified. Isolated pleomorphic cells are often present. (Right) Amyloid appears as an opaque, extracellular matrix material with a greenish appearance in Papanicolaou-stained alcohol-fixed smears such as this. The plasmacytoid cells with neuroendocrine chromatin are seen in the background.

Intranuclear Cytoplasmic Inclusions



RET Gene



(Left) An air-dried Diff-Quik stained preparation shows a mitosis, along with a couple of intranuclear cytoplasmic inclusions in this example of a medullary carcinoma FNA smear. (Right) The RET gene is known to be associated with medullary carcinoma development. Specific codons are known to be sites of mutations resulting in hereditary medullary thyroid carcinoma, as illustrated.

Spindle Cell Tumor With Thymus-Like Differentiation

KEY FACTS

TERMINOLOGY

- Biphasic tumor showing spindle-shaped epithelial cells that blend with glandular structures, showing primitive thymic differentiation

CLINICAL ISSUES

- Male > female (2:1)
- Most common in young patients (< 20 years)
- Commonly present with unilateral painless mass, often present for years
- Thyroidectomy with lymph node dissection if clinically positive
- Chemoradiation employed for metastatic disease
- Tumor has prolonged, indolent course
 - Late metastases obligates long-term follow-up
 - Significant metastatic disease: 70% of cases
 - All metastases should be removed since clinical course is prolonged

MICROSCOPIC

- Very cellular tumor with primitive thymus histology
- Lobules of tumor separated by acellular, sclerotic septa
- Most tumors are biphasic
 - Short, reticulated, intersecting and streaming, tight to loose fascicles or bundles
 - Blend with glandular and tubulopapillary structures
- Long, spindled cells with scant cytoplasm
- Pale-staining cuboidal to columnar cells lining cysts

ANCILLARY TESTS

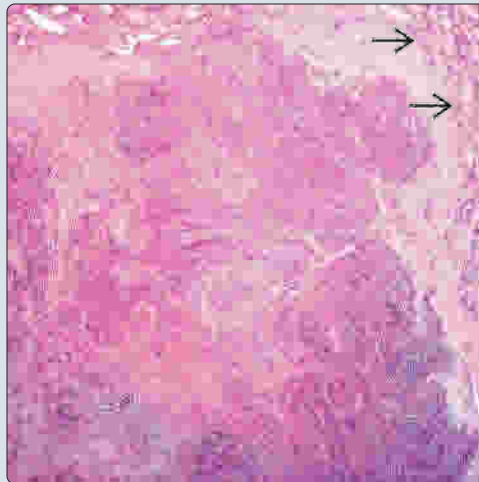
- **Positive:** AE1/AE3, CAM5.2, EMA, CK7, vimentin, CD117
- **Negative:** Thyroglobulin, TTF-1, calcitonin, CEA, CD5, S100 protein, synaptophysin, chromogranin, CK20

TOP DIFFERENTIAL DIAGNOSES

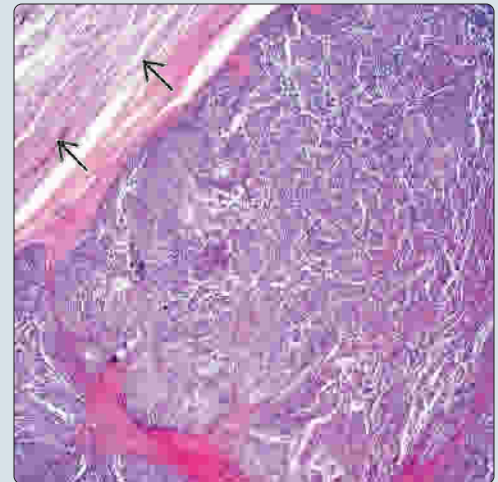
- Undifferentiated carcinoma, synovial sarcoma, medullary carcinoma, ectopic thymoma, smooth muscle tumors

Spindled Cells Separated From Thyroid

(Left) Sclerotic septa are noted to intersect between the lobules of tumor. A fibrous connective tissue capsule separates the tumor from the surrounding thyroid parenchyma. The spindled pattern of growth is easily identified, even at this magnification. **(Right)** There is a very cellular tumor with lobules of tumor separated from the thyroid follicular epithelial cells by a well-developed capsule. In this tumor, there are short, intersecting, and streaming bundles of tumor cells.

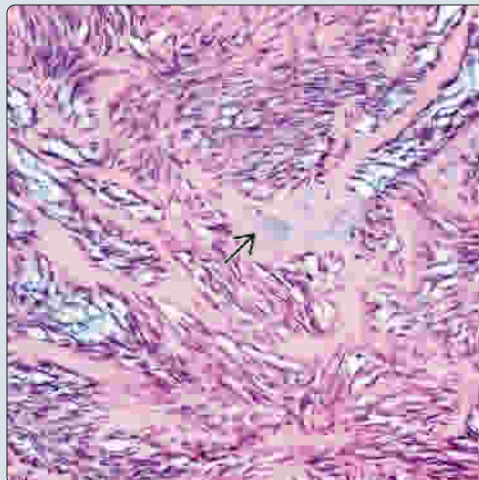


Cellular Tumor With Papillae

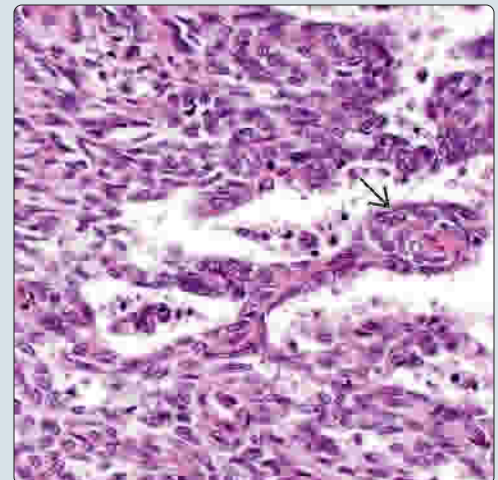


Mucinous Stroma and Streaming Fascicles

(Left) The acellular fibrous septa separate the spindled cells into streaming tight fascicles. The cells are monotonous and bland. There is a syncytial pattern without distinct cell borders. The stroma is slightly mucinous in this lesion. **(Right)** The biphasic appearance shows short, tight bundles of bland spindle cells blending with glandular and tubulopapillary structures. There is a high nuclear:cytoplasmic ratio with a syncytial appearance.



Spindled Cells With Tubulopapillary Projections



TERMINOLOGY

Definitions

- Biphasic tumor showing spindle-shaped epithelial cells that blend with glandular structures, showing primitive thymic differentiation

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Intrathyroidal ectopic thymic tissue
- Remnants of branchial pouches that retained ability to differentiate into thymic-type tumor

CLINICAL ISSUES

Epidemiology

- Age
 - Most common in young patients (< 20 years)
- Sex
 - Male > female (2:1)

Presentation

- Commonly present with painless mass
- Less frequently: Rapidly enlarging neck mass, localized tenderness (thyroiditis), tracheal compression
- Symptoms present for weeks to years

Treatment

- Late metastases obligates long-term follow-up
- Thyroidectomy with lymph node dissection if clinically positive
 - Resection of metastases achieves longer survival
- Chemoradiation employed for metastatic disease

Prognosis

- Tumor has prolonged, indolent course (~ 90% 5-year survival)
- Regional lymph node metastases at presentation
- Significant metastatic disease: 70% of cases
 - Delayed blood-borne metastases (up to 22 years later)
 - Lung, lymph nodes, kidney, soft tissues
 - All metastases should be excised, prolongs clinical course

MACROSCOPIC

General Features

- Variable: Encapsulated to partially circumscribed to infiltrative, vaguely lobular
- May show soft tissue adhesion (fat or skeletal muscle)
- Firm to hard, mainly solid; small cysts sometimes
- Gray-white to tan; yellow areas suggesting necrosis
- Gritty texture may be present

Size

- Range: 1-12 cm; mean: 3.6 cm

MICROSCOPIC

Histologic Features

- Very cellular tumor with primitive thymus histology
- Lobules of tumor separated by acellular, sclerotic septa
- Most tumors are biphasic

- Short, reticulated, intersecting and streaming, tight to loose fascicles or bundles
- Blend with glandular and tubulopapillary structures
- Long, spindled cells with scant cytoplasm
 - Syncytial whorling to storiform pattern without distinct cell borders
- Elongated nuclei with fine, delicate nuclear chromatin; focal pleomorphism
- Glandular structures
 - Large cystic spaces lined with respiratory epithelium
 - Mucinous glands, cords, nests, Sertoli-like tubules, glomeruloid structures
 - Pale-staining cuboidal to columnar cells, ciliated or goblet-like
 - Nuclei tend to be more round than spindle cells
- Scant mitoses; rarely necrosis and increased mitoses
- Vascular invasion may be present
- Intercellular fluid and mucin may be seen
- Squamous metaplasia or keratin pearls are exceptional
- Lymphocytes, often at periphery
- Calcifications are uncommon

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** AE1/AE3, CAM5.2, EMA, CK7, vimentin, CD117, INI1; **focal:** SMA, MSA, CD99
- **Negative:** Thyroglobulin, TTF-1, calcitonin, CEA, CD5, S100 protein, synaptophysin, chromogranin, CK20

DIFFERENTIAL DIAGNOSIS

Undifferentiated Carcinoma

- Tumor of old patients with rapidly enlarging infiltrative mass; marked pleomorphism, necrosis, mitoses
- **Positive:** Pan-cytokeratin, p63, pax-8

Synovial Sarcoma

- Young patients; often biphasic tumor with spindle cell population; TLE1(+); t(X;18) SS18-SSX2 gene fusion

Medullary Carcinoma

- Frequently contains stromal amyloid, with plasmacytoid cells showing salt and pepper chromatin
- **Positive:** Calcitonin, CEA-m, chromogranin, CD56

Ectopic Thymoma

- Jigsaw-puzzle-like lobulation with rich, immature TdT(+) T cell population

Smooth Muscle Tumors

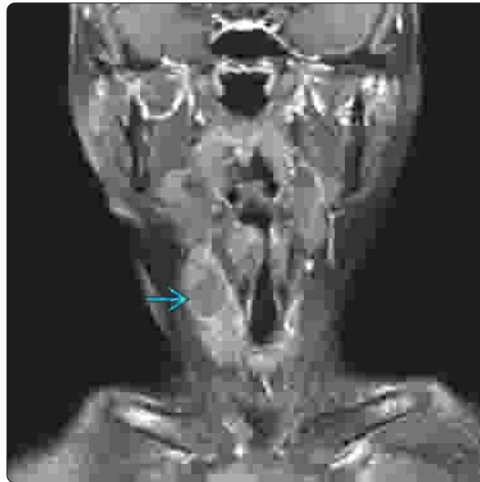
- Primary or metastatic; fascicular architecture with spindle tumor cells showing perinuclear clearing
- **Positive:** SMA, MSA, desmin

SELECTED REFERENCES

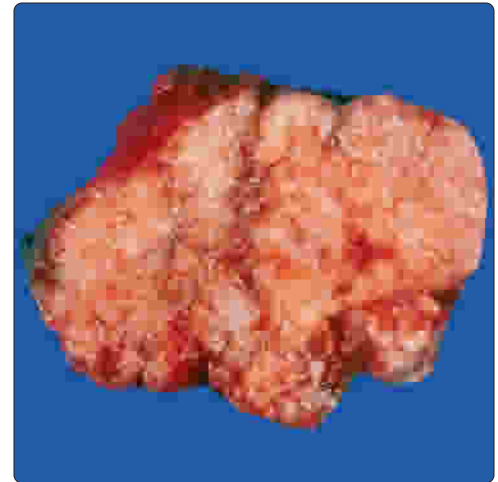
1. Folpe AL et al: Spindle epithelial tumor with thymus-like differentiation: a morphologic, immunohistochemical, and molecular genetic study of 11 cases. *Am J Surg Pathol.* 33(8):1179-86, 2009
2. Papi G et al: Primary spindle cell lesions of the thyroid gland; an overview. *Am J Clin Pathol.* 125 Suppl:S95-123, 2006
3. Chan JK et al: Tumors of the neck showing thymic or related branchial pouch differentiation: a unifying concept. *Hum Pathol.* 22(4):349-67, 1991

Tumor Mass in Thyroid Gland

(Left) This coronal MR T1 (postcontrast enhancement) shows a tumor mass [A] within the thyroid gland. There is lower uptake than the adjacent thyroid gland. This finding is nonspecific, however. (Right) The cut surface shows a fleshy tumor with invasion of the entire thyroid gland. There are cystic spaces with a shiny surface. (Courtesy X. Matias-Guiu, MD.)

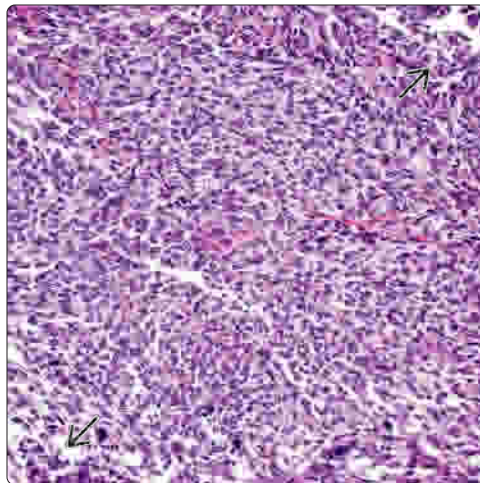


Fleshy Tumor Invading Thyroid Gland

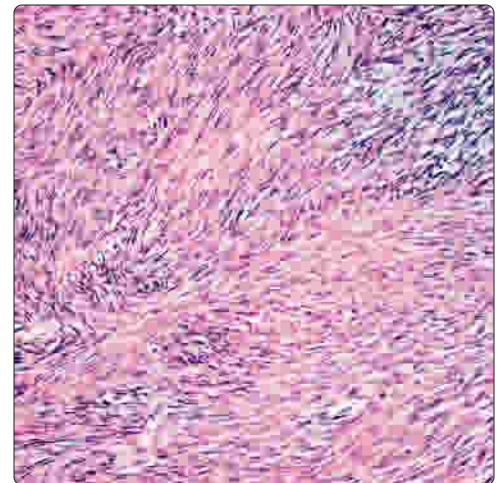


Spindled and Epithelioid Appearance

(Left) In this tumor, there is a more prominent epithelioid appearance to the spindled population. The syncytium shows areas of primitive glandular differentiation [A]. The cells have a high nuclear:cytoplasmic ratio. (Right) This field shows short, reticulated, intersecting and streaming, tight fascicles or bundles of bland, elongated spindled cells with scant cytoplasm. There are indistinct cell borders.



Short, Streaming, Tight Fascicles

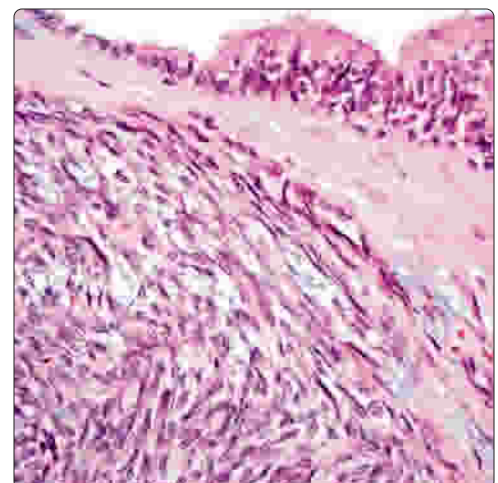


Sclerotic Septa Separate Tumor Lobules

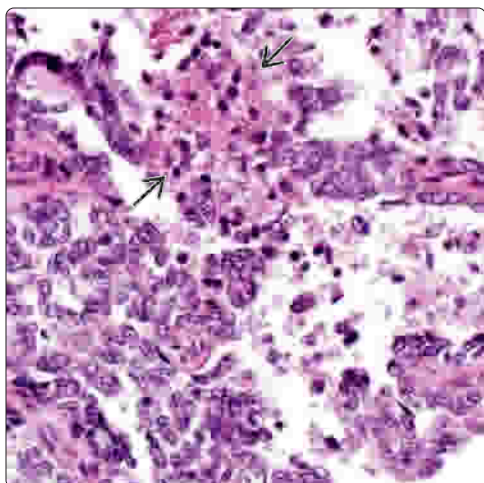
(Left) Lobules of tumor are separated by acellular, sclerotic fibrous septa. In this field, there are short fascicles, juxtaposed to the thyroid gland parenchyma [A]. (Right) Short bundles of spindled cells are separated by a mucinous material. The cystic space is lined by respiratory epithelium, showing pseudostratified columnar cells. The nuclei are rounder than the spindled population.



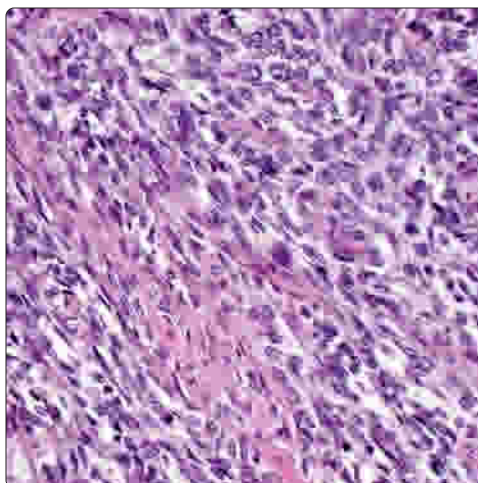
Spindled Cells and Respiratory-Type Epithelium



Tubulopapillary Structures With Necrosis

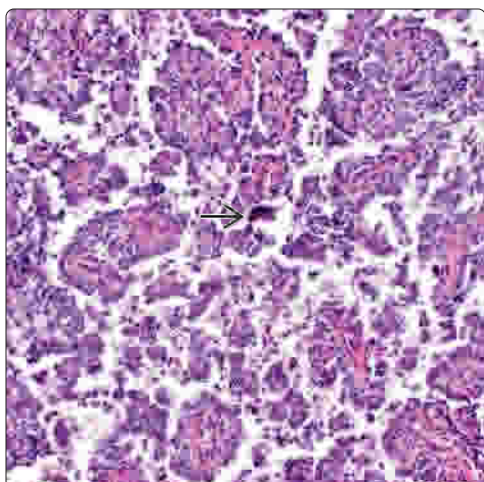


Loose Spindled Cells With Collagen

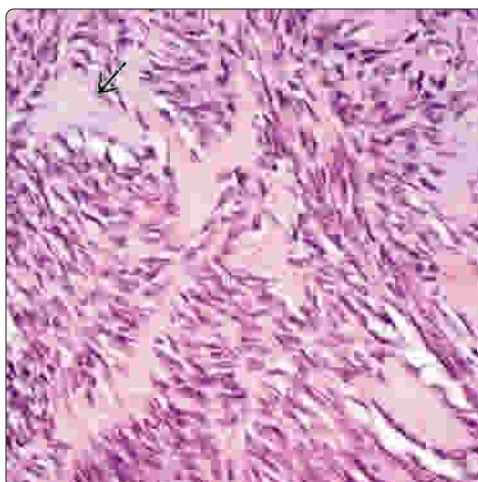


(Left) These glandular and tubulopapillary structures show an area of necrosis [] associated with slightly greater pleomorphism. The nuclei are still vesicular with delicate nuclear chromatin distribution. **(Right)** The spindled cells show a loose arrangement, with areas showing a more collagenized stromal deposition. The nuclei are oval with open chromatin.

Cystic Spaces and Rare Calcifications

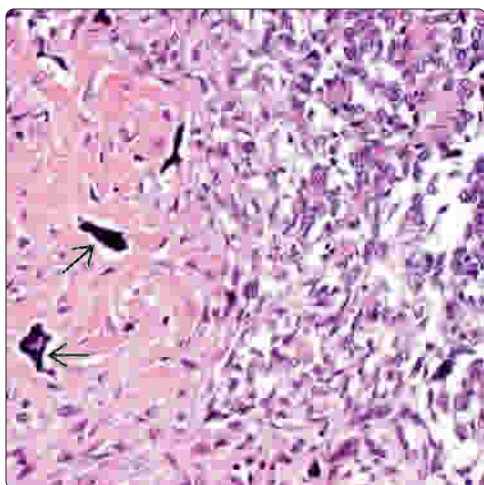


Bland Spindled Cells With Stroma

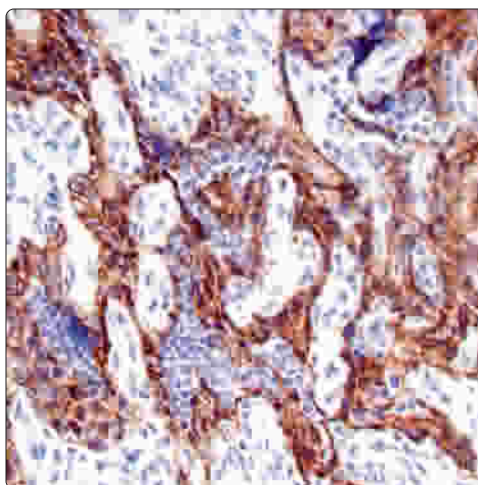


(Left) This area demonstrates the cystic spaces comprised of numerous tubulopapillary structures. The cells have pale-staining cuboidal to columnar cells lining the cysts. This field highlights an isolated calcification []. **(Right)** These bland spindled cells are arranged in short fascicles with collagenized to myxoid [] stroma. Mitoses are usually inconspicuous.

Focal Areas of Pleomorphism



CK-PAN Strongly Highlights Epithelial Cells



(Left) The fibrous septa contain highly pleomorphic tumor cells []. The remainder of the tumor exhibits blending of spindled and tubulopapillary structures, showing long, spindled cells with scant cytoplasm and limited pleomorphism. **(Right)** Many different epithelial markers are positive, but keratin highlights the spindled and epithelial cells. Some cells will also show reactions with actins. There is usually absent thyroglobulin, TTF-1, calcitonin, synaptophysin, and CDS.

KEY FACTS

TERMINOLOGY

- Primary thyroid gland malignancy that is architecturally and cytologically similar to thymic epithelial tumors

ETIOLOGY/PATHOGENESIS

- Persistence of cervical thymic tissue from embryologic development

CLINICAL ISSUES

- Most common in 5th decade
- Female > male (1.3:1)
- Vast majority in lower poles of thyroid gland
- Commonly present with painless thyroid mass
- Protracted course requires long-term follow-up
- Combination surgery, chemotherapy, and radiation

MICROSCOPIC

- Well circumscribed, slightly lobulated, and easily demarcated

- Extrathyroidal extension is common
- Broad, pushing, smooth-bordered islands
- Desmoplastic cellular stroma
- Tumor cells are squamoid and syncytial to spindled
- Well-defined cell borders, intercellular bridges, and frank keratinization are uncommon
- Nuclei are oval, with vesicular chromatin
- Lymphocytes and plasma cells present

ANCILLARY TESTS

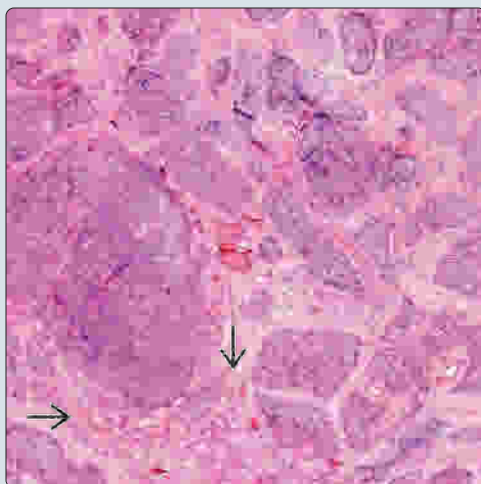
- **Positive:** Pancytokeratin (especially HMWK), p63, pax-8, CD5, CD117, GLUT-1, p53
- **Negative:** TTF-1, thyroglobulin, calcitonin, EBER

TOP DIFFERENTIAL DIAGNOSES

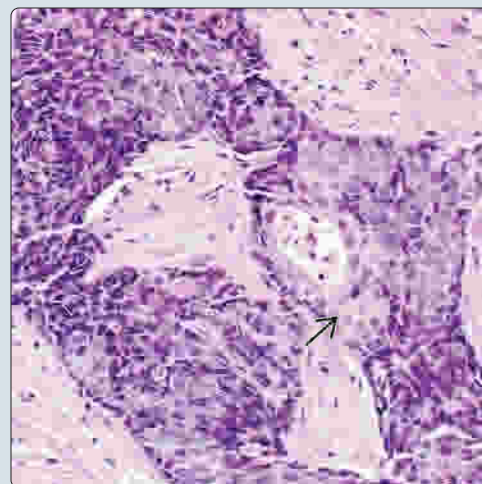
- Undifferentiated carcinoma, squamous cell carcinoma, medullary carcinoma, follicular dendritic cell sarcoma, primary thymic tumor, metastatic lymphoepithelial carcinoma, ectopic thymoma, ectopic hamartomatous thymoma, mucoepidermoid carcinoma

Invasive Lobules of Carcinoma

(Left) The thyroid parenchyma is infiltrated by the lobules of neoplastic epithelium. The tumor cells show well-demarcated islands separated by dense, hyalinized fibrous bands. This is a typical pattern for CASTLE. (Right) Note the bands of fibrosis at the periphery of the tumor island. A spindled morphology is present in this area. Intercellular bridges can be appreciated, a finding that helps with the diagnosis.

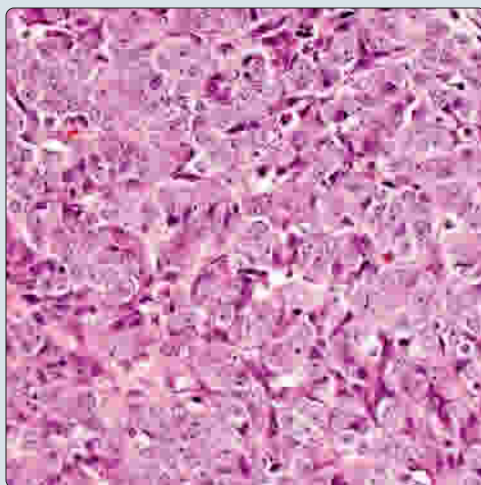


Squamous Differentiation and Spindling

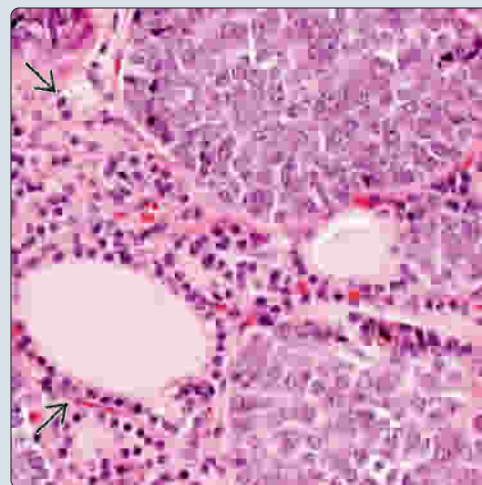


Lymphoepithelial-Like Pattern

(Left) This field shows a lymphoepithelial quality that can be seen in CASTLE. The tumor is nonkeratinizing, with an undifferentiated appearance. Note the vesicular nuclear chromatin with small nucleoli. (Right) The lobules of neoplastic cells show a syncytial appearance. The cells have a very high nuclear:cytoplasmic ratio, vesicular nuclear chromatin, and delicate nucleoli. The thyroid follicles are surrounded by the neoplastic proliferation.



Syncytial Appearance of Tumor Cells



TERMINOLOGY

Abbreviations

- Carcinoma showing thymus-like differentiation (CASTLE)

Synonyms

- Lymphoepithelioma-like carcinoma of thyroid gland
- Intrathyroid epithelial thymoma and primary thyroid thymoma

Definitions

- Primary thyroid gland malignancy that is architecturally and cytologically similar to thymic epithelial tumors

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Arises from thymic rests adjacent to or within thyroid gland
 - Persistence of cervical thymic tissue from embryologic development
 - Branchial pouch remnants (including solid cell nests) that can differentiate along thymic lines

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very rare (< 1% of all thyroid gland malignancies)
- Age
 - Most common in 5th decade
- Sex
 - Female > male (1.3:1)

Site

- Vast majority in lower poles of thyroid gland
 - Rare cases may arise in perithyroid soft tissues

Presentation

- Commonly present with painless thyroid mass
- Less frequently, patients present with tracheal compression, hoarseness
- Enlarged neck lymph nodes are seen in up to 30%
- Clinical associations with thymoma are **not** yet documented in CASTLE
 - e.g., myasthenia gravis, hypogammaglobulinemia, red-cell aplasia/hypoplasia, dermatomyositis

Treatment

- Options, risks, complications
 - Long-term clinical follow-up due to protracted clinical course
- Surgical approaches
 - Thyroidectomy is treatment of choice
 - Lymph node dissection in clinically positive neck
- Drugs
 - Neoadjuvant chemotherapy may achieve rapid relief of symptoms by decreased tumor size, permitting definitive surgery
- Radiation
 - Usually employed postoperatively
 - Patients receiving radiation tend not to develop locoregional recurrence

Prognosis

- Local recurrences seen in up to 30% of patients
- Cervical lymph node metastases in up to 30% of patients
 - Associated with worse prognosis
- Generally, good long-term prognosis
 - 10-year cause-specific survival: 82%
 - A few patients may experience rapidly fatal course

IMAGING

Radiographic Findings

- Scintigraphy shows cold nodule
- Computed tomography usually shows solid, noncalcified soft tissue density, perhaps with invasion
 - Slight enhancement with contrast material
- Appears as iso-/hypointense mass on T1-weighted MR and hyperintense on T2-weighted MR
- Ultrasound shows hypoechoic and heterogeneous mass

MACROSCOPIC

General Features

- Well circumscribed, slightly lobulated, easily demarcated, firm to fleshy, yellow, gray and tan

MICROSCOPIC

Histologic Features

- Similar to thymic carcinoma
- Extrathyroidal extension is common, including larynx and trachea
- Broad, pushing, smooth-bordered islands
 - Tumor cells are squamoid and syncytial to spindled
 - Well-defined cell borders, intercellular bridges, and frank keratinization are uncommon
 - Pale to eosinophilic cytoplasm
 - Nuclei are oval, show limited pleomorphism, and have fine pale to vesicular chromatin
 - Nucleoli are small, but easily identified
- Desmoplastic cellular stroma
- Tumor lobules associated with delicate vessels
- Lymphocytes and plasma cells present within tumor nests
- Mitotic figures are present but not increased (< 3/10 HPF)
- Hassall corpuscles may be seen (at tumor periphery)
- Granulomas are usually not identified

ANCILLARY TESTS

Cytology

- Cellular smears with atypical epithelial cells arranged in sheets, clusters and single cells (no follicles or papillae)
- Round or spindled tumor cells with distinct cell borders
- Nuclei have vesicular chromatin and prominent nucleoli; rare inclusions
- Lymphoid elements present in background

Immunohistochemistry

- **Positive:** Pancytokeratin (especially HMWK), p63, pax-8, CD5, CD117, GLUT-1, p53
- **Negative:** TTF-1, thyroglobulin, calcitonin, EBER

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CK-HMW-NOS	Positive	Cytoplasmic	All tumor cells, strong and diffuse
CK-PAN	Positive	Cytoplasmic	Nearly all tumor cells, strong and diffuse
CD5	Positive	Cytoplasmic	Nearly all tumor cells
p63	Positive	Nuclear	Most neoplastic cells
CEA-M	Positive	Cytoplasmic	Most neoplastic cells show reactivity
CD117	Positive	Cytoplasmic	Nearly all tumor cells
Mcl-1	Positive	Nuclear	Usually positive in most tumor cells
S100-A9	Positive	Nuclear & cytoplasmic	Isolated tumor cells will be positive
CD70	Positive	Cytoplasmic	Strong and diffuse positive
p53	Positive	Nuclear	Usually increased
EGFR	Positive	Cytoplasmic	Associated with mutations in a few cases
GLUT1	Positive	Cytoplasmic	Most tumor cells
E-cadherin	Positive	Cell membrane	Nearly all tumor cells
pax-8	Positive	Nuclear	Nearly all tumor cells
TTF-1	Negative		
Thyroglobulin	Negative		
Calcitonin	Negative		
EBER	Negative		
Chromogranin-A	Negative		

Electron Microscopy

- Elongated epithelial cells with prominent desmosomes, bundles of cytoplasmic tonofilaments, lacking secretory granules and amyloid fibers

DIFFERENTIAL DIAGNOSIS

Undifferentiated (Anaplastic) Carcinoma

- Significant invasion, remarkable pleomorphism, atypical mitotic figures, tumor necrosis
- **Positive:** Vimentin, cytokeratins

Squamous Cell Carcinoma

- Invasive tumor with significant keratinization, pearl formation, and intercellular bridges
- **Positive:** p63, CK5/6, p40, S100-A9; **negative:** CD5

Medullary Carcinoma

- Variable morphology, including plasmacytoid and spindled cells, with amyloid; background C-cell hyperplasia
- **Positive:** Calcitonin, chromogranin, CEA-M, CD56

Follicular Dendritic Cell Sarcoma

- Has lobular pattern, although infiltrating into thyroid tissue with extensive vascular invasion
- Syncytial arrangement of spindled to epithelioid cells
- Nuclear chromatin is vesicular with small, well-defined nucleoli
- **Positive:** CD21, CD23, CD35; **negative:** Keratin, CD5

Primary Thymic Neoplasm

- Direct invasion into thyroid from primary thymic neoplasm
- Radiographs and intraoperative findings should exclude continuity from thymic tumor

Metastatic Lymphoepithelial Carcinoma

- Primary site is most frequently nasopharynx but could be any other location (not thyroid primary)
- Lacks squamous differentiation, shows prominent nucleoli
- **Positive:** EBER, p63

Ectopic Thymoma

- Ectopic location of noninvasive, well-circumscribed, encapsulated tumor
- **Positive:** CD5, cytokeratin; **negative:** Bcl-2, Mcl-1

Ectopic Hamartomatous Thymoma

- Arises in low, anterior neck, but may appear thyroidal
- Unique pattern with adipose tissue and haphazard distribution of thymic tissues

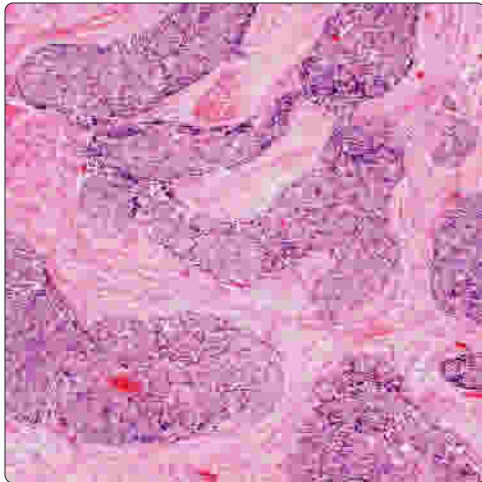
Mucoepidermoid Carcinoma

- Invasive tumor with transitional and epidermoid cells and mucocytes; often eosinophils; fibrosis; background chronic lymphocytic thyroiditis

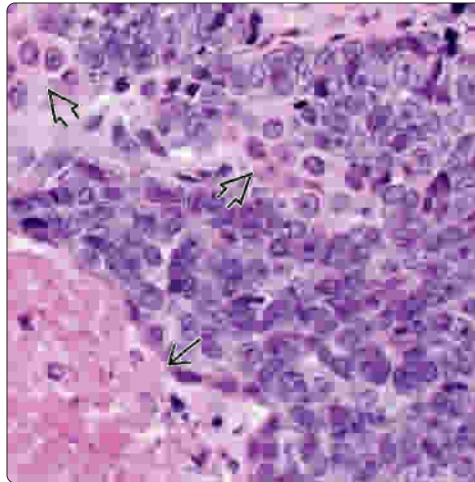
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Lobular Architecture With Bands of Fibrosis

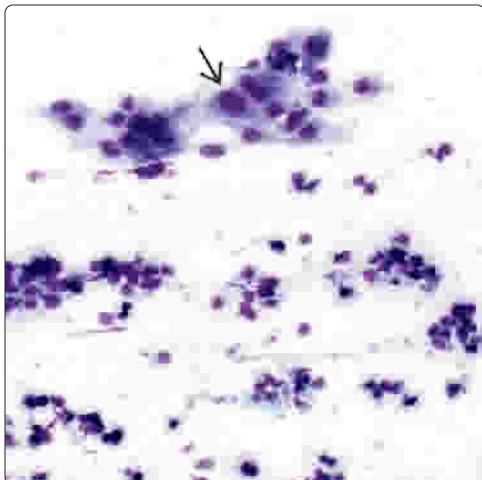


Necrosis and Focal Squamous Differentiation

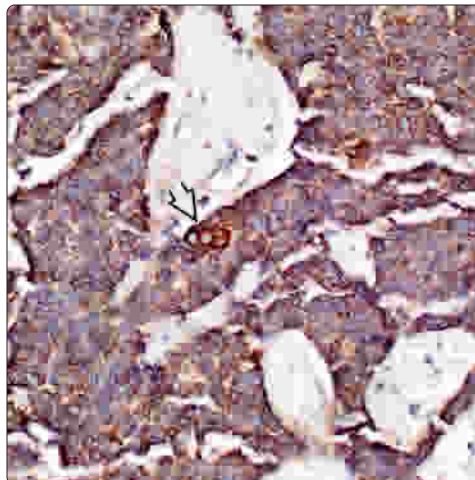


(Left) The low-power appearance of CASTLE is identical to thymic carcinoma, in which there is a distinctly lobular architecture and very heavy, dense, keloid-like collagenized fibrous bands. (Right) Syncytium of neoplastic cells with high nuclear:cytoplasmic ratio, vesicular chromatin, and prominent nucleoli is shown. There is necrosis [] and focal areas that show squamous differentiation [].

Dual Cell Population

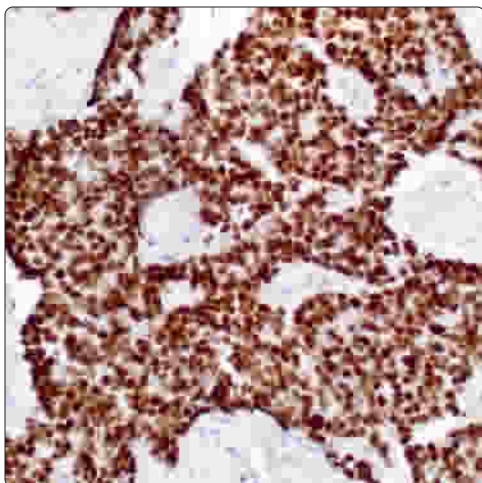


CK-PAN Strongly Highlights Squamous Areas

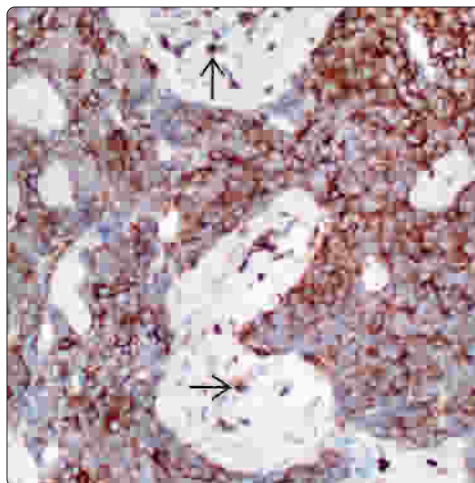


(Left) There is a cluster of epithelioid cells showing a much greater cell size [] than the uninvolved thyroid parenchyma. There is opacified cytoplasm in the slightly spindled cells. (Right) CK-PAN in this case stains all of the neoplastic cells with a moderate reaction, but strongly and diffusely highlights the areas of greater squamoid differentiation [].

p63 Strongly Highlights Neoplastic Cells



CD5 Reacts With Neoplastic Cells



(Left) p63 strongly and diffusely highlights all of the neoplastic cells in this CASTLE. It is not a specific marker in this case, but it does help to highlight all of the neoplastic cells. (Right) CD5 highlights most of the neoplastic cells in this example of a CASTLE. The CD5(+) lymphocytes [] are present in the background and serve as a positive internal control.

Mucoepidermoid Carcinoma

KEY FACTS

TERMINOLOGY

- Low-grade malignant thyroid tumor with histologic appearance similar to low-grade salivary gland counterpart

ETIOLOGY/PATHOGENESIS

- Likely origin from squamous metaplasia of follicular epithelial cells (possibly as a metaplastic variant of papillary carcinoma) supported on basis of

CLINICAL ISSUES

- Painless neck mass most common presenting complaint
- Surgery is treatment of choice
 - Conservative therapy (lobectomy or subtotal thyroidectomy) can be performed
- Indolent tumor with excellent prognosis

MICROSCOPIC

- Circumscribed but unencapsulated, infiltrative variably cystic and solid neoplasm
- **Squamous or epidermoid cells**

- Round to oval cells with round nuclei, prominent centrally located nucleoli, and eosinophilic cytoplasm
- Horny pearl formation, individual cell keratinization, and intercellular bridges

• **Mucous cells**

- Cells with abundant clear to foamy-appearing cytoplasm and peripherally located hyperchromatic nuclei

ANCILLARY TESTS

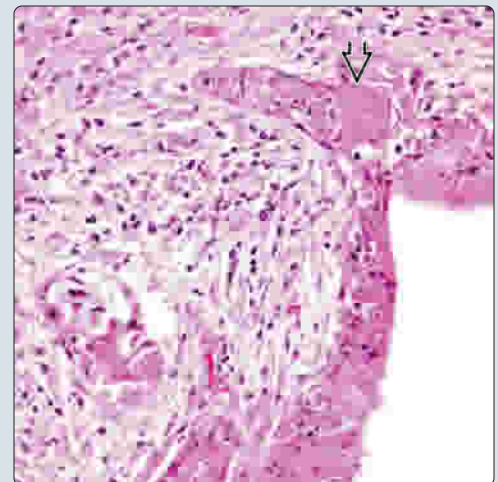
- Intracytoplasmic and intraluminal mucicarmine and DPAS positive material
- Immunohistochemistry
 - Epidermoid/squamous cells
 - Cytokeratins positive (High and low molecular weight, CK5/6); p63 may be present
 - Thyroglobulin, TTF-1 and pax-8 variably positive
- Genetics
 - Marked abnormalities of the cadherin/catenin complex
 - CRTC1/MAML2 fusion transcript reported

Infiltrative Neoplasm With Cystic Growth

(Left) Unencapsulated infiltrative intrathyroidal neoplastic proliferation predominantly cystic in growth with associated fibrosis. Focal lymphocytic thyroiditis is present in the adjacent thyroid parenchyma. (Right) Cystic and solid area of neoplasm exclusively comprised of the squamous or epidermoid cell component shows individual cell keratinization. Scattered mucocytes were present in other areas of the neoplasm (not shown).

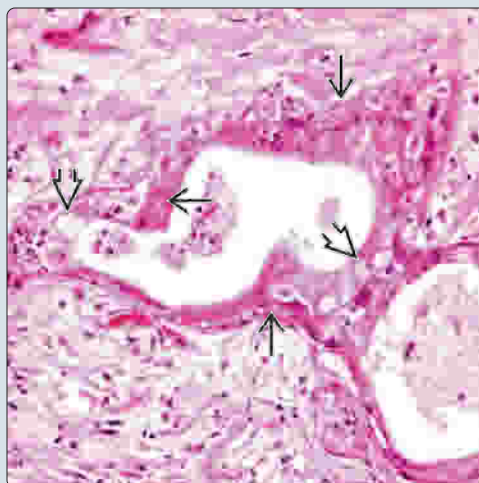


Epidermoid Cells



Epidermoid Cells and Mucocytes

(Left) The neoplastic proliferation includes an admixture of epidermoid/squamous cells with keratinization and mucocytes with clear appearing cytoplasm and peripherally located nucleus. (Right) Predominantly cystic epithelial cell lined neoplasm that includes mostly columnar cells with cilia, mucocytes and epidermoid cells (see next image for higher magnification).



Multicystic Growth



TERMINOLOGY

Abbreviations

- Mucoepidermoid carcinoma of thyroid gland (MECT)

Definitions

- Low-grade malignant thyroid tumor with histologic appearance similar to low-grade salivary gland counterpart
 - 2 histologic variants
 - Mucoepidermoid carcinoma
 - Sclerosing mucoepidermoid carcinoma with eosinophilia
 - Subclassification into 2 distinct entities appears justified based on apparent differences in light microscopic and immunohistochemical findings although this issue has not been entirely resolved;
 - Separation may be academic, since both tumor types share similar indolent biologic course

ETIOLOGY/PATHOGENESIS

Idiopathic

- No known etiologic factors
- History of radiation exposure during childhood reported in limited cases

Histogenesis

- Cell of origin for MECT subject of debate
- Likely origin from squamous metaplasia of follicular epithelial cells (possibly as a metaplastic variant of papillary carcinoma) supported on basis of
 - Transition from follicular epithelium or foci of papillary thyroid carcinoma
 - Occurrence in background of chronic lymphocytic (Hashimoto) thyroiditis
 - Common setting to find squamous metaplasia including presence of keratinization and intercellular bridges
 - Presence of thyroglobulin, TTF-1 and pax-8 reactivity
 - Presence of psammoma bodies
 - Indolent biology
 - Tendency to metastasize to regional lymph nodes
- Solid cell nests (SCN) of ultimobranchial origin (give rise to C-cells) considered progenitor based on some histologic, histochemical, and immunohistochemical (e.g., p63) features
 - SCN origin not favored based on
 - SCN lacking intercellular bridges
 - Absence of calcitonin, chromogranin immunoreactivity in MECT
 - Occurrence of MECT in isthmus and pyramidal lobes locations where SCNs not found
- Origin from thyroglossal duct

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon
 - Accounts for < 0.5% of all thyroid gland malignancies
- Age
 - Occurs over wide age range (2nd-8th decades)

- Most patients in 5th-7th decades of life

- Sex
 - Female > male

Site

- Any portion of thyroid gland including isthmus

Presentation

- Painless neck mass most common presenting complaint
- Less commonly, pain, hoarseness, vocal cord paralysis may occur
- Symptoms of tracheal, esophageal and recurrent laryngeal nerve compression may be present in presence of extrathyroidal extension

Laboratory Tests

- Patients are euthyroid

Treatment

- Surgical approaches
 - Surgery is treatment of choice
 - Conservative therapy (lobectomy or subtotal thyroidectomy) can be performed
 - In presence of extrathyroidal extension, total thyroidectomy advocated

Prognosis

- Indolent tumor with excellent prognosis
- Metastatic tumor to cervical lymph nodes may be seen
 - In up to 40% of patients
- Extrathyroidal extension in approximately 20%
- Distant metastasis is uncommon but may occur (e.g., lung, bone, pleura)
- Presence of extrathyroidal extension and metastatic disease does not appear to adversely affect prognosis in MECT
- Death from tumor may occur in older patients
 - Usually limited to cases with anaplastic (undifferentiated) component

IMAGING

Radiographic Findings

- Hypoactive ("cold") nodule on thyroid imaging

MACROSCOPIC

General Features

- Solitary demarcated but unencapsulated mass
 - May be infiltrative
 - Extrathyroidal extension may be identifiable
- Cut section shows
 - Solid, nodular appearance
 - Tan-brown to yellow-orange in color, rubbery to firm consistency
 - Cystic change sometimes with myxoid-mucoid appearance can be seen

Size

- May measure up to 3.5 cm in greatest dimension

MICROSCOPIC

Histologic Features

- Circumscribed but unencapsulated predominantly solid mass
 - Prominent cystic foci may be present
- Infiltrative with intertwined cords and nests of neoplastic cells in fibrous stroma
- Neoplastic proliferation includes squamous/epidermoid cells admixed with mucocytes
- **Squamous or epidermoid cells**
 - Round to oval cells with round nuclei, prominent centrally located nucleoli and eosinophilic cytoplasm
 - Horny pearl formation, individual cell keratinization and intercellular bridges
 - Mild nuclear pleomorphism, slight increase in nuclear to cytoplasmic ratio, scattered mitotic figures
- **Mucous cells**
 - Cells with abundant clear to foamy appearing cytoplasm and peripherally located hyperchromatic nuclei
 - Intimately admixed with squamous/epidermoid cells
 - Hyaline bodies resembling colloid may be seen in cytoplasm of mucocytes
- Columnar appearing cells with prominent cilia resembling respiratory-type epithelium can be identified
- Psammoma bodies occasionally present
- Intratumoral sclerosis composed of thick, acellular hyalinized bands of tissue can be seen
- Mixed inflammatory cell infiltrate including mature lymphocytes and plasma cells seen within neoplastic proliferation
 - Eosinophils may predominate in any given tumor
- Chronic lymphocytic thyroiditis commonly but not invariably present in surrounding nonneoplastic thyroid gland
 - May include foci of squamous metaplasia
- Generally confined to thyroid gland but extrathyroidal extension may occur
- Associated thyroid lesions that may be identified include:
 - Papillary thyroid carcinoma (separate or admixed) including tall cell variant
 - Concurrent PTC identified in up to 50% of cases
 - Areas of transition between MECT and PTC can be seen
 - Anaplastic carcinoma reported in association with PTC
 - Follicular carcinoma, conventional and oncocyctic variant
 - Adenomatoid nodules

ANCILLARY TESTS

Histochemistry

- Intracytoplasmic and intraluminal mucicarmine and DPAS positive material

Immunohistochemistry

- Epidermoid/squamous cells
 - Cytokeratins positive (high and low molecular weight, CK5/6)
 - p63 may be present
- Thyroglobulin, TTF-1 and pax-8 variably positive
 - Thyroglobulin staining may be focal or even absent

- Mucocytes
 - polyclonal carcinoembryonic antigen (CEA) expression may be identified
- Calcitonin, neuroendocrine markers negative

Genetic Testing

- Marked abnormalities of the cadherin/catenin complex, including consistent neoexpression of P-cadherin and major alterations in the expression of E-cadherin
- CRTC1/MAML2 fusion transcript reported
 - Commonly present in salivary gland MEC
- *BRAF* (V600E) mutation not detected

DIFFERENTIAL DIAGNOSIS

Squamous Metaplasia in Lymphocytic Thyroiditis

- Does not produce mass
- Absence of mucocytes

Epithelial Cysts in Lymphocytic Thyroiditis

- Predominantly lined by squamous epithelium
- Columnar (respiratory-type) epithelium can be seen, which may contain mucocytes that stain for mucin
- Almost invariably described in association with chronic lymphocytic thyroiditis
- Unifocal or multifocal without infiltrative growth or associated desmoplasia

Papillary Thyroid Carcinoma With Squamous Metaplasia

- Characteristic nuclear features diagnostic for papillary thyroid carcinoma
- Absence of mucocytes

Medullary Thyroid Carcinoma With Squamous Differentiation

- Presence of calcitonin, neuroendocrine markers

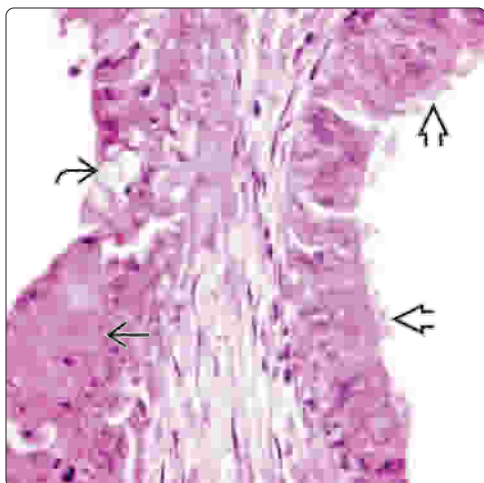
Primary Thyroid Squamous Cell Carcinoma

- Characterized by marked cytologic atypia
- Absence of mucocytes

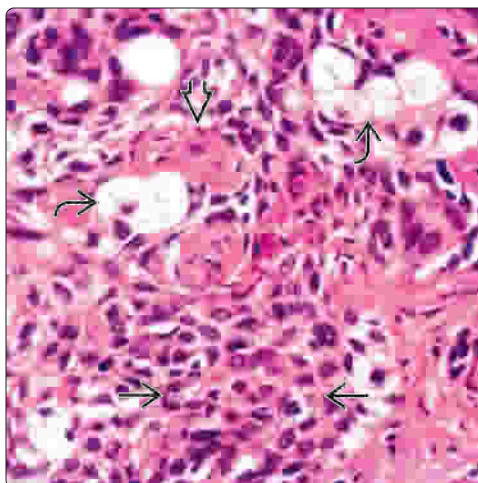
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Epidermoid Cells, Mucocytes and Ciliated Columnar Cells

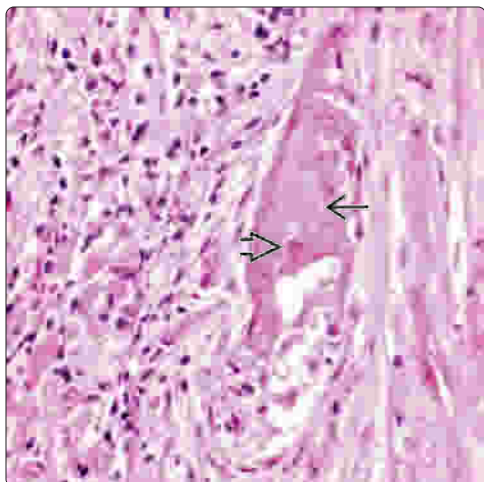


Solid Growth

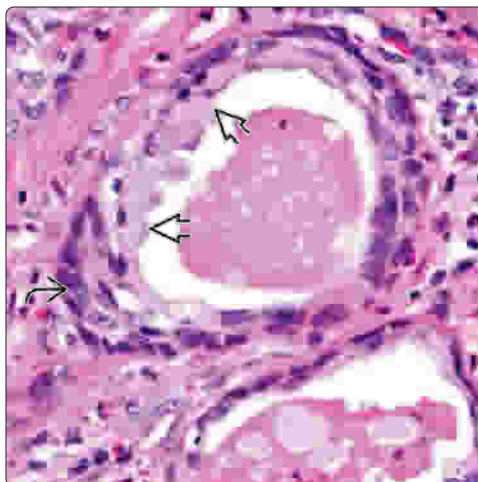


(Left) Cystic foci show squamous/epidermoid cells [] and admixed mucocytes []. The presence of ciliated cells [] has raised a possible (although unproven) branchial cleft derivation for MECT given histologic similarities to branchial cleft cysts. (Right) This tumor had predominantly solid growth mostly composed of epidermoid cells [] focally with keratinization [] as well as the presence of scattered intermixed mucocytes [].

Epidermoid Cells With Keratinization

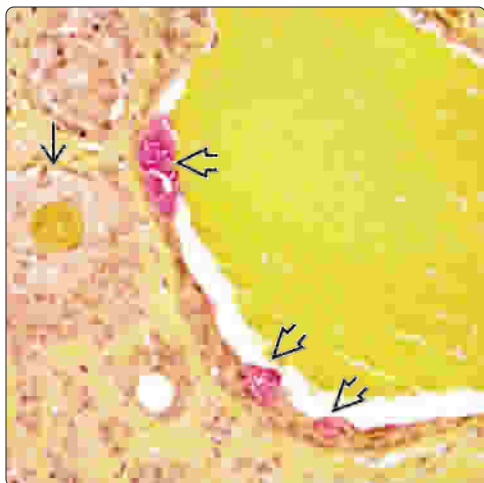


Mucocytes

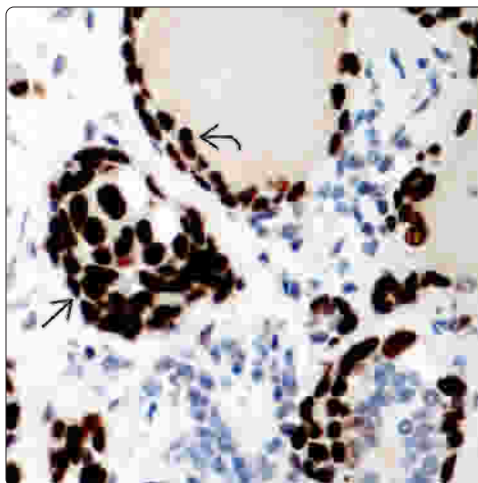


(Left) H&E shows infiltrative solid focus of tumor composed of squamous/epidermoid cells with keratinization, dyskeratotic cell [], and intercellular bridges [] with surrounding inflammatory cells. Scattered mucocytes were present in other areas of the neoplasm (not shown). (Right) Tumor nest composed of a greater number of mucocytes [] is characterized by abundant basophilic-appearing cytoplasm and peripherally placed nuclei. Squamous/epidermoid cells are seen along the periphery [].

Intracytoplasmic Mucin



TTF-1 Expression



(Left) Intracytoplasmic mucin positive material [] can be utilized in the identification &/or confirmation of mucocytes; adjacent solid tumor nests of squamous/epidermoid cells are mucicarmine negative []. (Right) The cyst lining cells [] and cells of the solid tumor nests [] show TTF-1 (nuclear) immunoreactivity. This finding along with thyroglobulin and PAX8 staining (not shown) support a follicular epithelial cell origin for MECT.

Sclerosing Mucoepidermoid Carcinoma With Eosinophilia

KEY FACTS

TERMINOLOGY

- Low-grade malignant thyroid tumor with histologic appearance similar to low-grade salivary gland counterpart, including
 - Squamous/epidermoid cells and mucous cell differentiation
 - Plus presence of prominent sclerotic stroma with eosinophil-rich inflammatory cell component

ETIOLOGY/PATHOGENESIS

- Presumed to arise from squamous metaplasia of thyroid follicular epithelium
 - Usually occurs in setting of chronic lymphocytic (Hashimoto) thyroiditis

CLINICAL ISSUES

- Slowly growing, painless neck mass
- Total thyroidectomy treatment of choice
- Excellent prognosis; generally follows indolent course

- Recent evidence suggests possibility of aggressive behavior

MICROSCOPIC

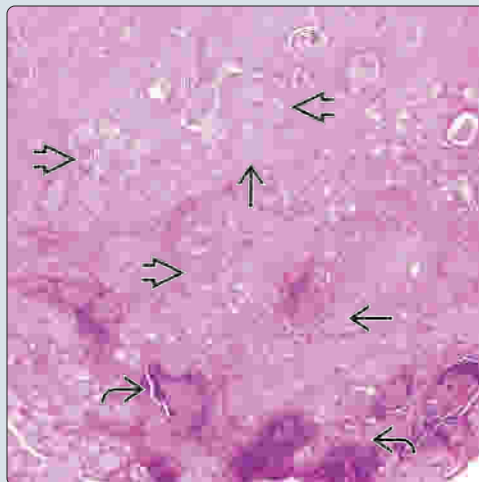
- Circumscribed but unencapsulated to infiltrative
- Anastomosing cords and narrow strands of tumor cells infiltrating sclerotic stroma with associated mixed inflammatory cell infiltrate that includes numerous eosinophils
- Squamous or epidermoid cells
- Mucous cells include scattered mucocytes
- Background changes of chronic lymphocytic (Hashimoto) thyroiditis that may include squamous metaplasia

ANCILLARY TESTS

- Cytokeratins, including CK19, galectin-3, TTF-1 (nuclear) all positive
- p63 strongly stains squamous/epidermoid cells
- Thyroglobulin typically negative but occasionally faint staining may be present

Unencapsulated Infiltrative Tumor

(Left) Thyroid tumor that is unencapsulated and infiltrative, composed of tumor nests with an associated sclerotic stroma, and occurs in the background of chronic lymphocytic (Hashimoto) thyroiditis is shown. (Right) Infiltrative tumor is predominantly composed of solid tumor nests of squamous/epidermoid cells, including keratinization occurring in association with chronic lymphocytic (Hashimoto) thyroiditis.

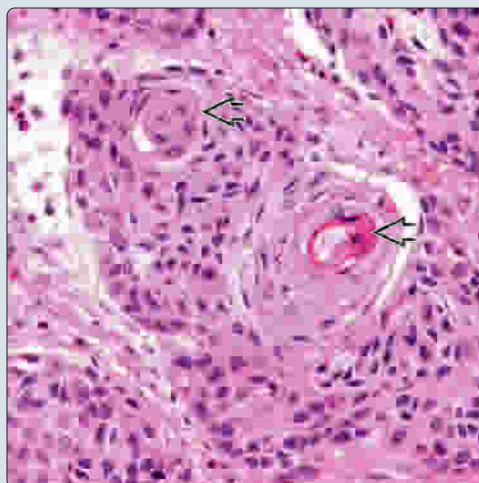


Solid Tumor Nests With Squamous Features

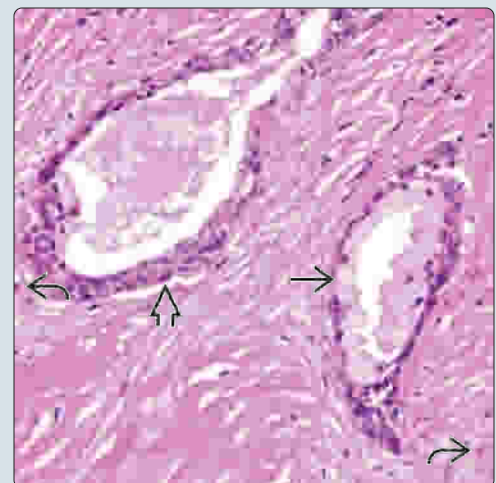


Squamous/Epidermoid Cells

(Left) Solid nests of squamous &/or epidermoid cells are shown, including cells with keratinization &/or clear spaces in between cells representing intercellular bridges. Inflammatory cells including eosinophils are present surrounding the tumor nests. (Right) Infiltrative tumor nests that include epidermoid cells and mucocytes are present within a densely sclerotic stroma that includes a sparse inflammatory cell infiltrate, including scattered eosinophils.



Sclerotic Stroma



TERMINOLOGY

Abbreviations

- Sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE)

Definitions

- Low-grade malignant thyroid tumor with histologic appearance similar to low-grade salivary gland counterpart, including
 - Squamous/epidermoid cells and mucous cell differentiation
 - Plus presence of prominent sclerotic stroma with eosinophil-rich inflammatory cell component
- Considered distinct from thyroid mucoepidermoid carcinoma

ETIOLOGY/PATHOGENESIS

Idiopathic

- No known etiologic agent

Histogenesis

- Presumed to arise from squamous metaplasia of thyroid follicular epithelium
 - Usually occurs in setting of chronic lymphocytic (Hashimoto) thyroiditis, fibrous variant
 - Presence of keratinization, intercellular bridges, TTF-1, and thyroglobulin reactivity
 - Absence of calcitonin and chromogranin reactivity
- Origin from ultimobranchial body (solid cell nests) suggested
 - Some histologic, histochemical, and immunohistochemical features suggest possible origin from solid cell nests
 - Presence of p63 expression raises possibility that these tumors originate from ultimobranchial body

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon thyroid neoplasm
- Age
 - Occurs over wide age range (2nd-8th decades)
 - Most patients in 5th-7th decades of life
- Sex
 - Female > male

Presentation

- Slowly growing, painless neck mass
- Rarely presents with rapid enlargement, hoarseness, or vocal fold paralysis
- May occur in any portion of thyroid gland including isthmus

Laboratory Tests

- Euthyroid

Treatment

- Surgical approaches
 - Total thyroidectomy treatment of choice, especially since extrathyroidal extension is common (~ 50% of cases)

Prognosis

- Indolent tumor with excellent prognosis
 - Recent evidence suggests possibility of aggressive behavior
- Metastatic tumor to cervical lymph nodes may be present
 - Occurs in up to 30% of cases at presentation
- Distant metastasis is uncommon but may occur to lung and bone

IMAGING

Radiographic Findings

- Hypoactive (cold) nodule on thyroid imaging

MACROSCOPIC

General Features

- Tumors usually appear as ill-defined, white to yellow, firm, solid mass ranging in size from 1-13 cm
 - Cystic change may occur, but this is uncommon

MICROSCOPIC

Histologic Features

- Circumscribed but unencapsulated to infiltrative
- Anastomosing cords and narrow strands of tumor cells infiltrating sclerotic stroma with associated mixed inflammatory cell infiltrate that includes
 - Prominent eosinophils as well as lymphocytes and plasma cells
- Neoplastic cells include
 - Squamous or epidermoid cells
 - Keratinization (keratin pearls, keratin debris) and intercellular bridges present
 - Mucous cells
 - Scattered mucocytes &/or less commonly mucin pools
- Clear cells may be seen
 - Represent minor component (10-30%)
 - Pseudoangiomatous appearance may be identified owing to loss of cohesion of tumor cells
- Chronic lymphocytic (Hashimoto) thyroiditis commonly present in surrounding nonneoplastic thyroid gland
 - May include foci of squamous metaplasia
- Papillary thyroid carcinoma (PTC) may be identified
 - Transition between SMECE and PTC may be identified but less common than in thyroid mucoepidermoid carcinoma
- Perineural and vascular invasion may be present

ANCILLARY TESTS

Histochemistry

- Mucin stains (mucicarmine and periodic acid-Schiff with diastase)
 - Intracytoplasmic and intraluminal mucin-positive material
 - Cystic spaces show mucin-positive material

Immunohistochemistry

- Cytokeratins, including CK19, galectin-3, TTF-1 (nuclear) all positive
- p63 strongly stains squamous/epidermoid cells

- Suggests possible origin from pluripotent solid cell nests
- Thyroglobulin typically negative but occasionally faint staining may be present
- Polyclonal carcinoembryonic antigen may be present in association with mucocytes
- Calcitonin, chromogranin, S100 protein, calponin, SMA all negative

DIFFERENTIAL DIAGNOSIS

Chronic Lymphocytic (Hashimoto) Thyroiditis With Squamous Metaplasia

- Tends not to form mass
- Lacks mucocytes, mucin pools, significant eosinophil cell component

Direct Extension of Carcinoma From Adjacent Organ

- Primary squamous cell carcinomas of larynx and esophagus can invade thyroid gland
- In general, clinical &/or radiographic evidence confirms presence of extrathyroidal cancer invading thyroid gland
- Absence of mucocytes &/or glandular differentiation

Undifferentiated (Anaplastic) Thyroid Carcinoma

- Characteristic demographics and clinical presentation including older aged patients with rapidly enlarging neck mass
- Histology characterized by presence of extensively infiltrative (intrathyroidal &/or extrathyroidal) high-grade undifferentiated malignant cells with
 - Increased mitotic activity, atypical mitoses, necrosis, angioinvasion
 - Necrosis
 - Lymph-vascular invasion
- Lacks mucocytes, mucin pools, significant eosinophil component

Squamous Cell Carcinoma

- Rare type of primary thyroid carcinoma
- Lacks mucocytes, mucin pools, significant eosinophil cell component

Carcinoma Showing Thymus-Like Differentiation

- Architecture shows some resemblance to lobulated appearance seen in thymic tumors (thymoma or thymic carcinoma) including
 - Solid nests or lobules with expansile or infiltrative growth into thyroid tissue in broad fronts
 - Dense fibrous bands creating lobulated or septated appearance
- Cellular composition similar to nasopharyngeal carcinoma, nonkeratinizing undifferentiated type including
 - Epithelioid cells with large, pleomorphic nuclei with vesicular chromatin, small distinct nucleoli, abundant eosinophilic cytoplasm with indistinct cell borders
- Mitotic activity seen on order of 1-2 mitoses per 10 HPF
- Squamous differentiation may be present, including
 - Keratinization, intercellular bridges, foci of abrupt keratinization (resembling Hassall corpuscle)
- May have mucinous material
- Lacks mucocytes, mucin pools, and significant eosinophilic component
- Unique immunohistochemical profile including

- Cytokeratin positive
- Thyroglobulin, TTF-1, calcitonin all negative
- CD5 positive
- CD117 (CKIT) reactivity also present
- EBV negative

Hodgkin Lymphoma

- Rarely, primary Hodgkin disease of thyroid may occur
 - Hodgkin disease involving thyroid usually occurs secondary to cervical or mediastinal nodal disease
- Nodular sclerosing most common histologic type

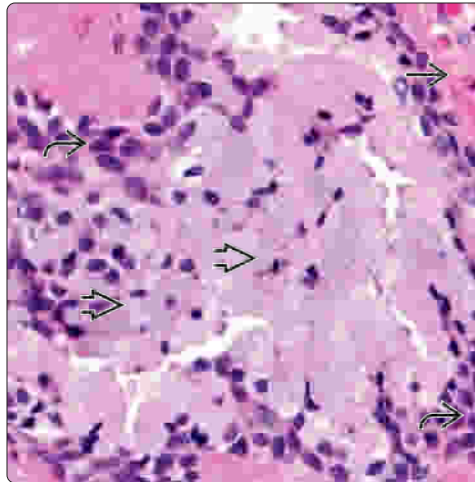
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Squamous/Epidermoid Cells

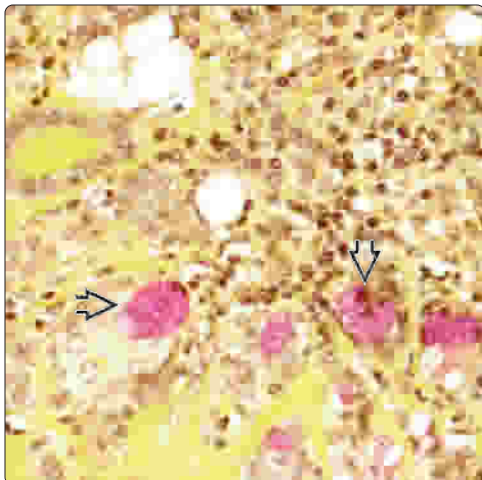


Mucous Cells

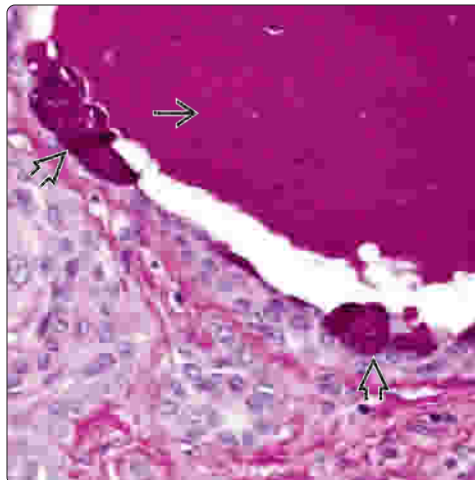


(Left) Solid tumor nest is entirely composed of squamous/epidermoid cells characterized by keratinization [red box] and intercellular bridges [blue box]; associated sclerosis [green box] and eosinophils [yellow box] are present around the tumor nests. (Right) Tumor nest almost entirely composed of mucocytes characterized by cells with abundant basophilic-appearing cytoplasm [red box] is shown. Squamous/epidermoid cells [blue box] are focally seen. Sclerotic stroma with eosinophils [yellow box] are present around the tumor.

Mucicarmine-Positive Mucous Cells

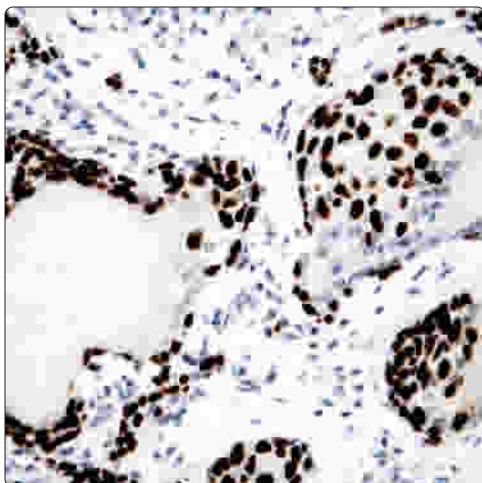


Periodic Acid-Schiff With Diastase-Positive Mucocytes

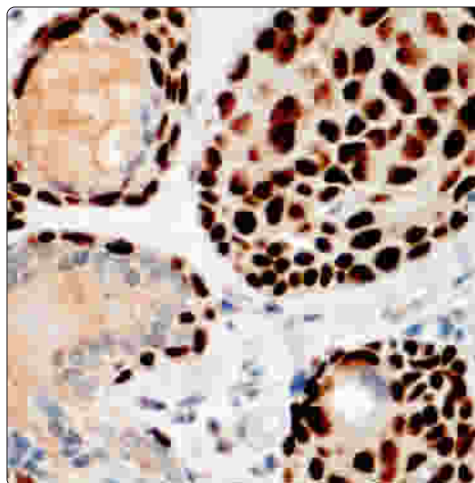


(Left) Histochemical staining assists in confirming the presence of mucocytes as seen by the presence of intracytoplasmic mucicarmine-positive material [red box]. (Right) In addition to mucicarmine staining, periodic acid-Schiff with diastase (DPAS) staining assists in identifying and confirming the presence of mucocytes as evidenced by the presence of intracytoplasmic diastase-resistant, PAS-positive material [red box]. Intraluminal DPAS positive material is also present [red box].

TTF-1 Immunoreactivity



p63 Immunoreactivity



(Left) Lesional cells show strong nuclear TTF-1 reactivity. Thyroglobulin staining is typically negative but may occasionally show faint focal staining (not shown). (Right) Tumor nests of squamous/epidermoid cells are p63 (nuclear) immunoreactive. The tumor cells were also variably immunoreactive for TTF-1 and thyroglobulin (not shown), supporting the follicular epithelial cell origin, although the presence of p63 raises the possibility of origin from pluripotent solid cell nests.

KEY FACTS

TERMINOLOGY

- Thyroid primary squamous cell carcinoma (SCC) is composed entirely of squamous cells without mucocytes & without direct invasion from adjacent organs (larynx, esophagus)

CLINICAL ISSUES

- Rare: < 1% of malignant thyroid tumors
- Mean age: 63 years (range: 24-90 years)
- Female > male (2:1)
- Patients present with rapidly enlarging anterior neck mass
- Early radical resection yields best prognosis
- Radical-dose external beam radiotherapy
- Tumors follow rapidly fulminant course: Mean: 9 months

MACROSCOPIC

- Extrathyroidal extension is common (72%)
- Large: Up to 12 cm

MICROSCOPIC

- Must always exclude direct extension: Larynx, esophagus
- Widely invasive tumor, destroying thyroid parenchyma
- Cohesive cells arranged in sheets, ribbons, nests
 - Polygonal, polyhedral, & spindle tumor cells
- Keratinization & keratin pearl formation
- High mitotic index, including atypical forms
- Classified as keratinizing or nonkeratinizing

ANCILLARY TESTS

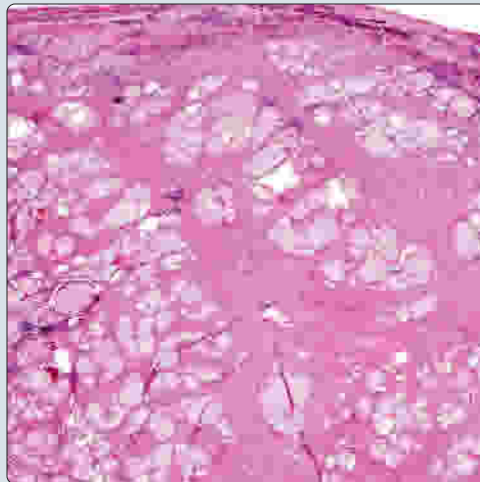
- **Positive:** Pancytokeratin, CK5/6, p63, p40
- **Negative:** Thyroglobulin, CEA, calcitonin, CD5

TOP DIFFERENTIAL DIAGNOSES

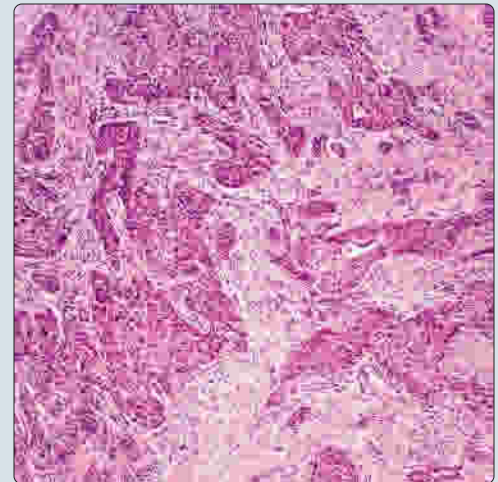
- Direct extension from adjacent organs, metastatic SCC, extensive squamous metaplasia within other thyroid lesion, carcinoma showing thymus-like differentiation (CASTLE), mucoepidermoid carcinoma, undifferentiated carcinoma

Widely Infiltrative Squamous Cell Carcinoma

(Left) The thyroid gland is nearly completely replaced by a widely infiltrating tumor. The tumor type is not identifiable at this magnification, but effacement of the thyroid gland is obvious. **(Right)** There is a desmoplastic stroma separating the neoplastic islands of this squamous cell carcinoma (SCC) of the thyroid. There is a nested, sheet-like, and individual cell infiltration by the neoplastic cells.

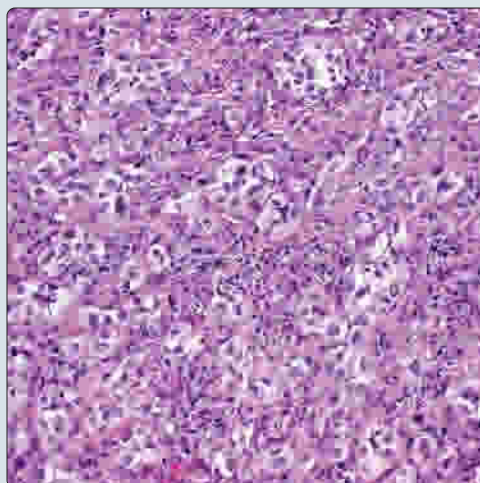


Islands of Squamous Cell Carcinoma

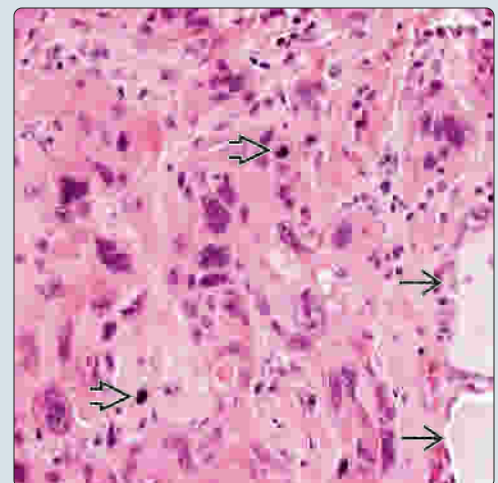


Epithelioid Cells in Desmoplastic Stroma

(Left) There are large epithelioid cells arranged in sheets and nests within this thyroid gland, associated with marked desmoplasia. There is no keratinization or dyskeratosis in this field. **(Right)** The squamous epithelium shows profound nuclear pleomorphism. There is dyskeratosis and keratinization. Thyroid follicles are noted at the periphery [box]. Mitotic figures are present [box].



Mitoses in Squamous Cell Carcinoma



TERMINOLOGY

Abbreviations

- Squamous cell carcinoma (SCC)

Definitions

- Thyroid primary SCC is composed entirely of squamous cells without mucocytes & without direct invasion from adjacent organs (larynx, esophagus)

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Radiation history is occasionally present

Pathogenesis

- Derived from thyroid follicular epithelium
 - Directly or via squamous metaplasia, then additional alterations to reach malignant tumor
- Persistence of thyroglossal duct or branchial pouch embryonic remnants

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare: < 1% of malignant thyroid tumors
- Age
 - Mean: 63 years (range: 24-90 years)
- Sex
 - Female > male (2:1)

Presentation

- Patients present with rapidly enlarging anterior neck mass
 - Many have preexisting thyroid disease (chronic lymphocytic thyroiditis)
- Frequent recurrent laryngeal nerve compression & pressure symptoms
 - Airway obstruction, dyspnea, dysphagia
 - Direct involvement of nerves, vessels, & soft tissues
- Cervical lymph node enlargement is common
- Paraneoplastic syndrome is rare
 - Hypercalcemia, fever, & leukocytosis
 - Probably develops as result of tumor-derived humoral mediators

Endoscopic Findings

- Endoscopic evaluation (laryngoscopy, esophagoscopy, bronchoscopy) to exclude direct extension

Treatment

- Options, risks, complications
 - Airway collapse & esophagotracheal fistula may complicate course
- Surgical approaches
 - Early radical resection yields best prognosis (multivariate analysis)
- Drugs
 - Thyroid hormone suppression may help
 - Thyroid-stimulating hormone may be growth factor
 - Chemotherapy does **not** alter disease course
- Radiation
 - Radical-dose external beam radiotherapy

- Radiation alone for unresectable tumors &/or poor surgical candidates
- Radioiodine therapy does **not** work

Prognosis

- Nearly all patients present with advanced disease
- Tumors follow rapidly fulminant course
 - Prognosis is poor; median survival: 9 months; 3-year survival: < 20%
 - Localized disease only; managed aggressively, patients may survive longer
 - Airway compromise results in death
- Local invasion & lymph node metastases is common
- Distant metastasis (lung) is less common (~ 30%)

IMAGING

Radiographic Findings

- Large mass, often showing necrosis &/or calcification
- Radiographic studies exclude direct invasion from contiguous organs

MACROSCOPIC

General Features

- Firm, tan-white mass involving 1 or both lobes
 - Multiple nodules of tumor can be seen
- Extrathyroidal extension is common (72%)
- Necrosis is common

Size

- Large: Up to 12 cm

MICROSCOPIC

Histologic Features

- Must always exclude direct extension (larynx, esophagus)
- Widely invasive tumor, destroying thyroid parenchyma
- Vascular & perineural invasion is common
- Cohesive cells arranged in sheets, ribbons, nests
- There is variable pleomorphism
- Polygonal, polyhedral, & spindle tumor cells
- Keratinization & keratin pearl formation, well-developed cell borders (intercellular bridges)
- High mitotic index, including atypical forms
- Classified as keratinizing or nonkeratinizing
- Inflammatory infiltrate & stromal fibroplasia often present
 - Association with Hashimoto thyroiditis is often well developed
- Other tumors may be present: Papillary carcinoma, follicular carcinoma, follicular adenoma
 - By convention, if another tumor is present, it is diagnosed with squamous differentiation incorporated into diagnosis

ANCILLARY TESTS

Cytology

- Confirm site of FNA (thyroid, larynx, lymph node, esophagus, metastasis) before diagnosis
 - FNA accuracy of < 30% primarily due to site uncertainty
- Background filled with necrotic & granular, eosinophilic keratin debris

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CK-PAN	Positive	Cytoplasmic	All tumor cells
CK5/6	Positive	Cytoplasmic	Nearly all tumor cells
CK19	Positive	Cytoplasmic	Nearly all tumor cells
p63	Positive	Nuclear	Most of the tumor cells
p40	Positive	Nuclear	Most of the tumor cells
CK7	Positive	Cytoplasmic	Weak and focal or patchy reactivity
CK18	Positive	Cytoplasmic	Weak and focal or patchy reactivity
EMA	Positive	Cytoplasmic	Weak and focal or patchy reactivity
TTF-1	Positive	Nuclear	Strong, but only focal tumor nuclei reactivity
S100-A9	Positive	Cytoplasmic	Diffuse, laminated positive in most tumor cells
p53	Positive	Nuclear	Increased reactivity as tumor becomes less differentiated
Thyroglobulin	Negative		
Calcitonin	Negative		
CEA-M	Negative		
CD5	Negative		

- Cellular smears contain cohesive clusters & isolated cells
- Irregular shapes (tadpole cells), nuclear hyperchromasia, & cytoplasmic orangeophilia & dyskeratosis

Immunohistochemistry

- **Positive:** Pancytokeratin, CK5/6, p63, p40
- **Negative:** Thyroglobulin, TTF-1, CEA, calcitonin, CD5

Genetic Testing

- Abnormal p53 expression & loss of p21 expression
 - p53 expression is greater in tumors with less squamous differentiation

DIFFERENTIAL DIAGNOSIS

Direct Extension From Adjacent Organs

- Much more frequent than primary thyroid SCC
- Bulk of tumor is centered in larynx, esophagus, or trachea
 - ~ 11% of radical laryngectomies (T3/T4) show direct thyroid invasion, especially in subglottic primaries
- Confirmed endoscopically, radiographically, or during surgery
- Primary thyroid SCC have much worse prognosis than tumors with direct extension
- Primary malignancy detected before thyroid involvement

Metastatic Squamous Cell Carcinoma

- Different primary site known clinically
 - Usually develops within 3 years of primary site documentation
- Tend to be multifocal, with high lymphovascular invasion

Extensive Squamous Metaplasia

- Squamous differentiation can be seen in lymphocytic thyroiditis, adenomatoid nodules, papillary carcinoma (diffuse sclerosing variant), undifferentiated carcinoma
- Tends to be focal, does not form mass clinically; lacks infiltration, cytologic atypia, & necrosis
- Squamous metaplasia **does not** predispose to SCC

Carcinoma Showing Thymus-Like Differentiation

- Greater degree of tumor spindling, has more keloid-like collagen deposition, & inflammatory cells
- **Positive:** CD5, S100-A9

Mucoepidermoid Carcinoma

- Epidermoid & transitional areas have mucocytes
- Tends to lack true keratinization & pearl formation
- Eosinophils may also be present

Undifferentiated Carcinoma

- Widely infiltrative, sheet-like to fascicular; poorly differentiated, pleomorphic, epithelioid cells; squamoid features may be seen, especially when primary thyroid carcinoma is present
- Significant immunohistochemistry overlap; management/prognosis are similar

STAGING

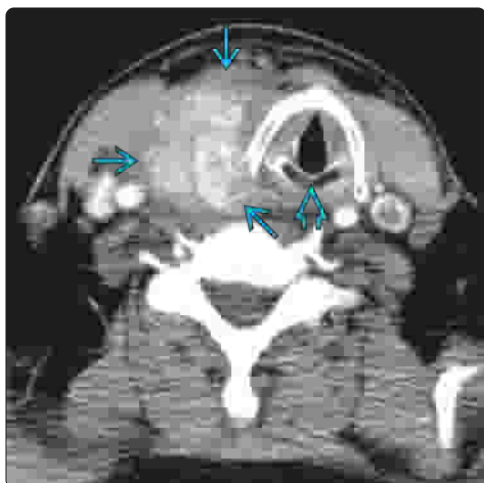
Thyroid AJCC Staging

- SCC is staged as undifferentiated carcinoma (at least pT4)

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Large Destructive Tumor of Thyroid

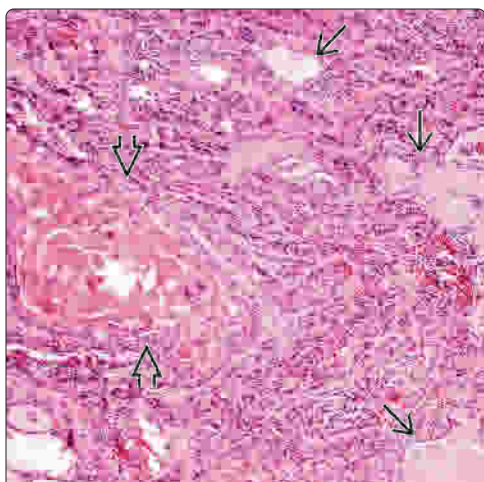


Nodules of Invasive Tumor

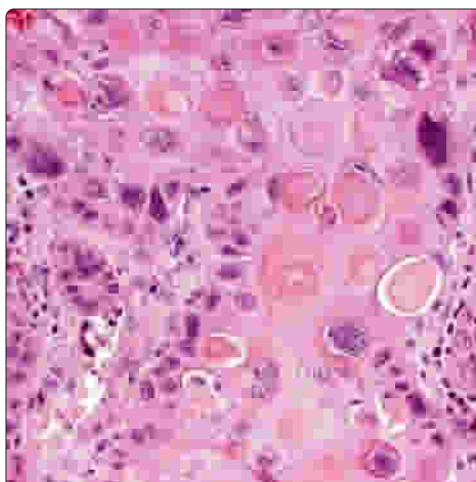


(Left) Radiographic images are used to highlight the extent of tumor and specifically to exclude invasion from the adjacent larynx or esophagus. In this case, there is a large mass replacing the right thyroid lobe. (Right) There are nodules of invasive SCC that are associated with the thyroid gland parenchyma. Note the background of chronic lymphocytic thyroiditis in the background of this case.

Keratinaceous Debris

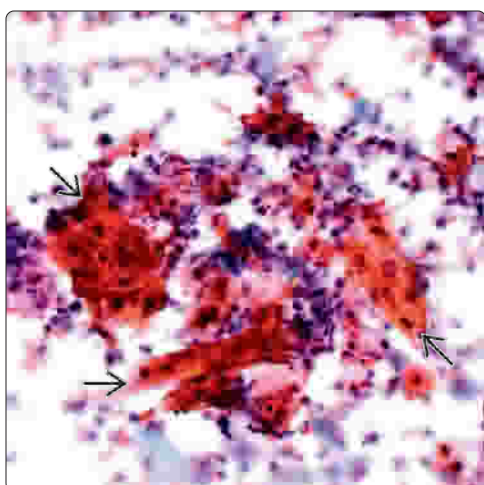


Dyskeratotic Cells

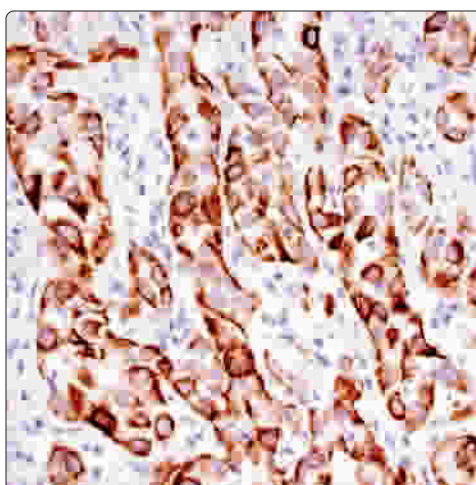


(Left) Keratin pearl formation with keratinaceous debris is noted within this SCC. There is extensive infiltration and destruction of the follicular epithelium. (Right) There is dyskeratosis and keratin pearl formation in this field, along with significant pleomorphism in the neoplastic cells. Well-developed cell borders are noted.

Keratinizing Squamous Cell Carcinoma Cells



Strong, Diffuse, CK5/6 Immunoreactivity



(Left) Smears show marked variation in cell size and shape with spindled and tadpole cells with dense orangeophilic cytoplasm, characteristic of squamous differentiation. The cells contain nuclei with dense chromatin. There is a background of inflammatory elements. Confirmation of the site of the sample is required. (Right) The neoplastic cells are strongly and diffusely highlighted with CK5/6, although, in general, immunohistochemistry is not required for the diagnosis. Other markers, such as p63 and p40, are also reactive.

KEY FACTS

TERMINOLOGY

- Primary thyroid lymphoma comprising heterogeneous group of tumors, usually associated with lymphocytic thyroiditis
 - Nearly all arise within chronic lymphocytic thyroiditis
 - 80x increased risk

CLINICAL ISSUES

- ~ 2-5% of all thyroid gland neoplasms
- Mean age: 65 years
- Female >>> male (3-7:1)
- Patients usually present with stage IE or IIE
- Adjuvant chemotherapy and radiation
- Mortality is grade and stage dependent
 - Overall, 85% 5-year survival

MICROSCOPIC

- Soft to firm, lobular, bulging cut surface, "fish flesh"
- Thyroid gland effaced by atypical lymphoid cells

- Lymphoepithelial lesions (LELs) are diagnostic
- **EMZBCL**: Vague nodularity to diffuse effacement
 - Colonization or follicle lysis by neoplastic B cells
 - Atypical small lymphocytes, marginal zone cells, monocytoid B cells, immunoblasts and centroblast-like cells, plasma cells
- **DLBCL**: Diffuse, large, atypical cells with increased mitotic figures

ANCILLARY TESTS

- Usually B cell immunophenotype (CD20, CD79a, pax-5)
- Keratin highlights lymphoepithelial lesions

TOP DIFFERENTIAL DIAGNOSES

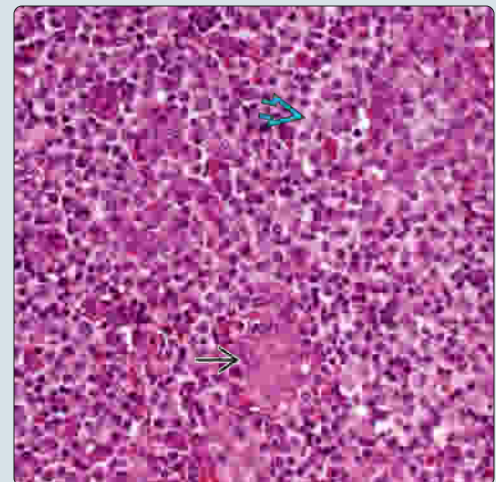
- Chronic lymphocytic thyroiditis
- Undifferentiated (anaplastic) carcinoma
- Ectopic thymoma
- Melanoma
- Sclerosing mucoepidermoid carcinoma with eosinophilia

Nodular Architectural Effacement

(Left) There are several greatly enlarged nodules of lymphocytes that are noted to destroy and efface the normal architecture of the thyroid gland. There is a background of chronic lymphocytic thyroiditis. (Right) This field shows a sheet-like monotonous population of monocytoid B cells, showing abundant, pale cytoplasm with lobulated or kidney-shaped nuclei. A single thyroid gland follicle is noted.

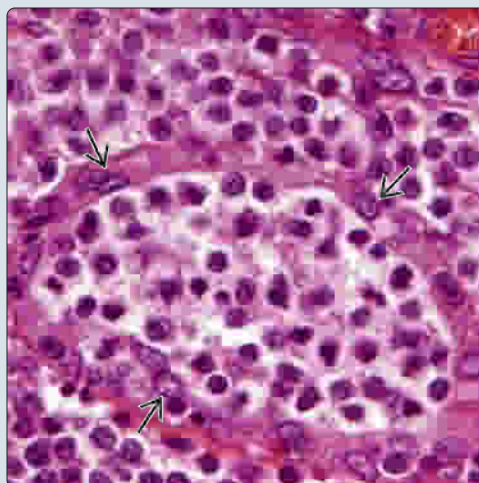


Monocytoid B-Cell Population

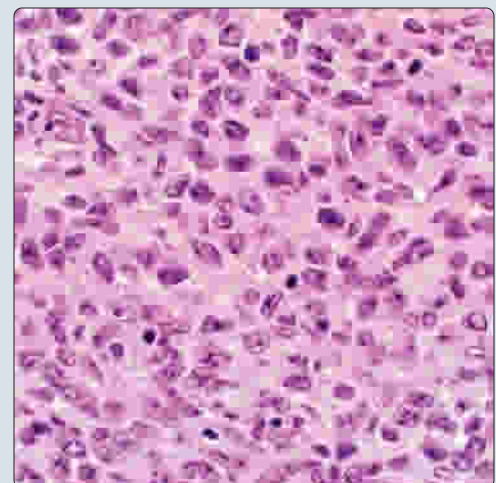


MALT Ball of Monocytoid B Cells

(Left) A MALT ball is a rounded ball or mass of atypical lymphoid cells (in this example monocytoid B cells), filling and distending the lumen of thyroid follicles (the follicular epithelium is marked). (Right) Sheets of a single type of large cell can be seen in DLBCL. While uncommon, these cells have a monocytoid B cell appearance. Mitotic figures are noted, and cytologic pleomorphism is moderate.



Sheets of Atypical Monocytoid Cells



TERMINOLOGY

Abbreviations

- Diffuse large B-cell lymphoma (DLBCL)
- Extranodal marginal zone B-cell lymphoma (EMZBCL)

Definitions

- Primary lymphoma arising within thyroid gland, usually associated with lymphocytic thyroiditis, comprising heterogeneous group of tumors
 - Mucosa-associated lymphoid tissue (MALT) is setting for development of extranodal marginal zone B-cell lymphoma, which may transform into DLBCL
 - Lack systemic involvement: Regional lymph nodes may occasionally be affected
 - **Rare:** Follicular lymphoma (FL), extramedullary plasmacytoma, T-cell lymphoma, Hodgkin lymphoma

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Carcinogenesis is multistep, multifactorial process with progressive accumulation of genetic changes
- Nearly all lymphomas arise in setting of chronic lymphocytic thyroiditis (Hashimoto disease)
- Acquired MALT from autoimmune/immune deficiency or inflammatory process
 - Nodular or diffuse infiltrate of lymphoid cells, frequently with follicles and germinal centers, and oncocyctic metaplasia of thyroid epithelium
 - Fibrosis and epithelial atrophy supports chronicity
- MALT lymphoma shows increased ratio of CD8(+) cells (suppressor/cytotoxic cell) to CD4(+) cells (helper/inducer cell) as compared to lymphocytic thyroiditis
- MALT lymphoma cell of origin is from postgerminal center, marginal zone B cells

CLINICAL ISSUES

Epidemiology

- Incidence
 - Uncommon
 - ~ 2-5% of all thyroid gland neoplasms
 - ~ 2-3% of all extranodal lymphomas
 - EMZBCL: < 2% of all extranodal lymphomas
 - DLBCL: ~ 15%
 - Relative risk of developing a lymphoma is **80x** greater in patients with chronic lymphocytic thyroiditis (compared to age- and sex-matched controls)
 - ~ 1% of Hashimoto patients develop lymphoma
- Age
 - Mean: 65 years; wide range: 14-90 years
- Sex
 - Female > > > male (3-7:1)

Site

- Must exclude secondary involvement of thyroid gland
 - Neck or mediastinal lymph nodes affected by lymphoma directly extending into thyroid gland
 - Yields different staging and management

Presentation

- Mass or goiter, often with recent rapid enlargement

- Causes obstructive symptoms related to compression
- Dysphagia, dyspnea, pain, and hoarseness
 - ~ 30% of patients
- Hypothyroidism (associated with Hashimoto thyroiditis)
 - Rarely, hyperthyroidism due to follicle destruction
- Associated cervical adenopathy in some cases
- Choking, coughing, and hemoptysis are uncommon
- Symptoms are usually present for short duration
 - **EMZBCL:** mean 6-12 months
 - **DLBCL:** mean 4 months
- Patients usually present with stage IE or IIE
- Patients usually lack B symptoms
 - Fever, profound night sweats, weight loss, anorexia

Laboratory Tests

- Antithyroid serum antibodies usually present
- Most patients are euthyroid

Treatment

- Options, risks, complications
 - Surgery for debulking and tissue diagnosis
 - Radiation may result in mucositis, hypothyroidism, and radiation pneumonitis
 - Single modality for IE/IIE disease and EMZBCL; multimodality therapy for IIIE/IVE and DLBCL
- Surgical approaches
 - Obtain tissue for diagnosis: Core needle or partial lobectomy
- Adjuvant therapy
 - Chemotherapy and radiation after appropriate classification through needle biopsy
 - DLBCL: Combined modality therapy
- Drugs
 - Chemotherapy regimens based on histologic type, grade, and stage
 - EMZBCL: Oral chlorambucil or intravenous chemotherapy
 - DLBCL: Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy
- Radiation
 - Based on histologic type, grade, and stage
 - EMZBCL: Single modality radiation therapy (usually up to 40 Gy)
 - Involved field only or extended field radiotherapy; latter associated with lower rates of local recurrence or relapse
 - DLBCL: Hyperfractionated radiation
- New modalities
 - Anti-CD20 (rituximab) combination therapy and new forms of immunotherapy hold promise

Prognosis

- Mortality is grade and stage dependent
- Overall, approximately 85% 5-year survival, although grade and stage dependent
 - Stage IE or IIE, low-grade histology: > 95% 5-year disease specific survival (DSS)
 - Stage IE or IIE, DLBCL: 50-70% 5-yr DSS
 - Stage IVE: ~ 30% 5-yr DSS
- Poor prognostic features include

- Age > 65 years, male, dysphagia (vocal cord paralysis), B symptoms
- High stage (IIIE, IVE), lymph node involvement
- Tumor histology (DLBCL > FL > EMZBCL)
- Extrathyroidal extension (large tumor size), vascular invasion, diffuse architecture, high mitotic rate
- Combined modalities: Lower relapse rate, reduced distant recurrence, least side effects
- Most patients present at stage IE or IIE (extranodal)
 - DLBCL: More likely to have stage IIIE or IVE
- If disseminated, most frequently involved sites are
 - Regional (cervical), mediastinal, and abdominal lymph nodes
 - Less common: Bone marrow, gastrointestinal tract, lung, bladder, and liver

IMAGING

Radiographic Findings

- Ultrasound
 - Marked hypoechoic, asymmetrical pseudocystic mass compared with residual thyroid tissue (linear echogenic strands or segmental patterns)
- Computed tomography
 - Heterogeneous mass, sometimes with cystic change
- Radioisotopic scan
 - F-18 FDG PET/CT maximum standardized uptake value [SUV(max)] was significantly higher in lymphoma (25 vs. 7) than lymphocytic thyroiditis

MACROSCOPIC

General Features

- May affect one or both lobes
- Soft to firm, lobular and multinodular appearance
- Effacement of normal thyroid with solid and cystic areas
- Cut surface: Bulging, smooth, pale-tan, "fish flesh"
- Usually homogeneous or mottled
- Extension into perithyroidal soft tissues

Size

- Wide variation, up to 20 cm

MICROSCOPIC

Histologic Features

- Nearly constant background of chronic lymphocytic thyroiditis
- Effacement of normal thyroid gland parenchyma
 - Ranges from vague nodularity to diffuse effacement
- Extension beyond thyroid gland into fat and skeletal muscle in about 50% of cases
- Lymphoepithelial lesions (LELs) are diagnostic
 - Atypical lymphoid cells infiltrating **and** destroying thyroid follicular epithelium
 - 2 types
 - **MALT balls:** Rounded balls or masses, filling and distending lumen of thyroid follicles
 - **Lymphoepithelial lesion:** Single or aggregated lymphocytes within or between follicular epithelial cells
- Lymph-vascular invasion common in high-grade tumors

- Atrophy of residual thyroid parenchyma and fibrosis
- Uninvolved thyroid parenchyma: May have adenomatoid nodules, adenomas, or foci of carcinoma (papillary > > > follicular > medullary)
- Vast majority are B-cell lymphomas: EMZBCL and DLBCL with transitions between them
 - Single or multifocal areas of large cell transformation adjacent to low-grade component

Extranodal Marginal Zone B-Cell Lymphoma (~ 54%)

- EMZBCL of MALT ± large cell component
 - Low-grade tumor by definition
 - Composed of heterogeneous population of B cells
 - Vague nodularity to diffuse effacement
 - Single or multifocal zones of large cell transformation
 - Transition from low- to high-grade morphology is easy to identify in most cases
- 20-30% of all thyroid gland lymphomas
- Background of chronic lymphocytic thyroiditis in almost all cases
- Reactive germinal centers, ± follicle colonization, are invariably present
 - Colonization or follicle lysis by neoplastic B cells
 - These cells yield darker zone within follicles on low power
 - Follicular architecture may mimic follicle center cell lymphoma
- Heterogeneous B cells include
 - Atypical small lymphocytes, marginal zone (centrocyte-like) small cleaved cells, monocytoid B cells, scattered large immunoblasts and centroblast-like cells, and plasma cells
 - Monocytoid B cells are monotonous population of atypical lymphoid cells with abundant, pale cytoplasm with lobulated or kidney-shaped nuclei
 - Small collections of monocytoid cells can be seen
- Dutcher bodies and Russell bodies easily identified
 - Cytoplasmic immunoglobulin (Mott cells) and striking plasmacytoid differentiation may simulate plasmacytoma
 - Crystal-storing histiocytes may be seen
- LELs easily identified
 - Keratin(s) highlights LELs
- Increased proliferation index usually within germinal center regions
- Infrequently, concurrent disease of gastrointestinal tract, salivary gland, orbit, lung, skin, or breast

Diffuse Large B-Cell Lymphoma (~ 45%)

- Diffuse, large, atypical cells with increased mitotic figures suggests transformation into diffuse large B-cell lymphoma
- ~ 45% of all thyroid gland lymphomas (although higher when transformation occurs)
- Perithyroidal extension into fat or skeletal muscle
- Vascular invasion is often seen
- Sheets of large, atypical lymphoid cells destroying thyroid parenchyma
 - Transitions between EMZBCL and DLBCL are common
 - However, may occur in absence of low-grade areas
- Large cells have spectrum of cytologic features

- Centrobasts, immunoblasts, monocytoid B cells, and plasmacytoid cells
- Focal Reed-Sternberg-like cells can be seen
- Burkitt-like growth with brisk mitotic activity, apoptosis, starry sky pattern
- Atrophy of residual thyroid parenchyma and fibrosis are often noted

Extramedullary Plasmacytoma (< 1%)

- Solitary extramedullary plasmacytoma (EMP)
 - No evidence of bone marrow involvement (excludes multiple myeloma)
- Very rare in thyroid
 - Most cases are probably EMZBCL with extensive plasma cell differentiation
- Sheets of plasma cells that may form nodules
 - Germinal center colonization or diffuse sheets of plasma cells around follicles
- Light chain restriction demonstrates monoclonality

Hodgkin Lymphoma (< 1%)

- Classical Hodgkin lymphoma, nodular sclerosis subtype is only one identified in thyroid gland
- Exceedingly rare
- Classical Hodgkin-Reed-Sternberg (HRS) cells identified in variably cellular background diathesis of plasma cells, eosinophils, and neutrophils
 - Lacunar and mummified variant HRS cells
- Birefringent collagen banding (stromal fibrosis), nodular pattern, and epithelioid histiocytes
- HRS cells: CD45RB negative, CD30 and CD15 positive
 - May coexpress B-cell markers (CD20), follicle center cell markers (CD10, Bcl-x, Bcl-2), and fascin, CD138, and EMA
- HRS-like cells can be seen in DLBCL (but they lack specific immunohistochemistry profile)

Follicular Lymphoma (FL) (< 1%)

- Considered primarily nodal-based lymphoma
- Exceedingly rare
 - Follicular pattern in EMZBCL: Current classification probably excludes FL
- Thyroid effacement by back to back neoplastic germinal centers with attenuated/absent mantle zones
- Monotonous population of centrocytes &/or centroblasts without tingible body macrophages
- CD10 and Bcl-6 highlight neoplastic germinal centers and possible diffuse component

Primary Peripheral T-Cell Lymphoma (< 1%)

- Exceedingly rare, but often associated with leukemic involvement
- Histologic, immunophenotypic, and molecular support required for diagnosis
- **Positive:** CD3, CD4, CXCR3; loss of 6q24-2

ANCILLARY TESTS

Cytology

- Fine-needle aspiration (FNA) may not work as well for diffuse thyroid enlargement
- Cellular aspirates, which may resemble chronic lymphocytic thyroiditis
 - Thyroid follicular epithelium is usually absent

- Dispersed, noncohesive admixture of lymphocytes, centrocytes, monocytoid B cells, immunoblasts, plasma cells, and histiocytes
 - Cytologic atypia may be present but tends to be limited in EMZBCL
 - No tingible body macrophages
- Monotonously atypical population of large cells with vesicular nuclear chromatin and prominent nucleoli and background lymphoglandular bodies suggests DLBCL
 - Cells are 2-3x size of mature lymphocytes
 - Necrosis is infrequently present
- Immunohistochemistry, flow cytometry, &/or Ig heavy chain gene rearrangements can be performed on aspiration material

Immunohistochemistry

- Usually B-cell immunophenotype (CD20, CD79a, pax-5)
 - κ or λ light chain restriction
- Keratin highlights lymphoepithelial lesions
- Germinal center follicular dendritic cells are disrupted or aborted

Flow Cytometry

- May be used to separate specific lymphoid populations

Genetic Testing

- Different B-cell clones dominating at different times, suggesting oligoclonal B-cell proliferation
 - Immunoglobulin heavy and light chain variable genes (*VH* and *VL*) expressed by MALT lymphomas show numerous point mutations in both *VH* and *VL* genes that are different relative to germline genes
 - Intracлонаl sequence heterogeneity, indicating ongoing somatic hypermutation
 - *Ig* gene hypermutation occurs at post germinal center stage of B-cell development
- Gene rearrangements for *IgVH* and *VL*, and for T-cell receptor β -chain genes are detected in lymphocytic thyroiditis
 - Different families of *VH* genes are detected in different lymphoma types
 - DLBCL shows *VH3*
 - EMZBCL shows *VH4* and *VH3*
- MALT lymphoma-associated translocations constitutively activate nuclear factor- κ B (NF- κ B) oncogenic pathway
 - t(11;18)(q21;q21), t(1;14)(p22;q32), t(14;18)(q32;q21), and t(3;14)(p14.1;q32), but seem to be mutually exclusive
 - Immunoglobulin heavy chain locus (IgH) is rearranged on chromosome 14, with forkhead box protein P1 (*FOXP1*)
- Aberrant p15, p16, and p73 promoter methylation is quite common
- *TP53* mutation followed by complete inactivation by loss of 2nd allele may be associated with high-grade transformation

DIFFERENTIAL DIAGNOSIS

Chronic Lymphocytic Thyroiditis

- No lymphoepithelial lesions (MALT balls) or cytologic atypia
- Not a diffuse process, although usually multifocal
- No germinal center colonization or destruction (perifollicular Bcl-2 reaction)

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CD20	Positive	Cytoplasmic	Dominant reaction in B-cell lymphomatous lymphocytes
CD79-α	Positive	Cytoplasmic	Especially in plasmacytoid cells
CD138	Positive	Cytoplasmic	May highlight plasmacytoid cells
κ light chain	Positive	Cytoplasmic	Restriction of either κ or λ in EMZBCL
λ light chain	Positive	Cytoplasmic	Restriction of either κ or λ in EMZBCL
Bcl-2	Positive	Cytoplasmic	In neoplastic, colonizing cells (negative image of normal germinal centers)
CD10	Positive	Cell membrane and cytoplasm	May be present in neoplastic lymphocytes (particularly FL)
CD43	Positive	Cytoplasmic	Coexpressed with CD20 in selected cases
CD45RA	Positive	Cytoplasmic	Coexpressed with CD20 in selected cases
Bcl-6	Positive	Nuclear	Identified more often in DLBCL and in FL
Ki-67	Positive	Nuclear	Variable, although highest in DLBCL
CD43	Positive	Cytoplasmic	Coexpressed with CD20(+) B cells in ~ 17% of MALT lymphoma
pax-5	Positive	Nuclear	Coexpressed in B cells
CK-PAN	Negative		Highlights destroyed thyroid follicular epithelium, especially lymphoepithelial lesions
CD3	Negative		Unless T-cell lymphoma
Cyclin-D1	Negative		Unless mantle cell lymphoma

- Oncocytic change in thyroid follicular epithelium
- Lack of Dutcher bodies
- In rare cases, IHC, flow cytometric, or molecular genetic analyses may be required
 - No light chain restriction; lacks CD10 and Bcl-6

Undifferentiated (Anaplastic) Carcinoma

- Cohesive to dyscohesive highly atypical epithelioid infiltrate
- May have concurrent epithelial tumor present (papillary or follicular carcinoma)
- Distinction from DLBCL may require immunohistochemistry
 - **Positive:** Cytokeratin; **negative:** CD45RB, CD20

Ectopic Thymoma

- Combination of epithelial and lymphoid elements
 - Not lymphoepithelial lesion
 - Nondestructive pattern
- **Positive:** Epithelial and T-cell antigens (CD5)

Melanoma

- Rare to have melanoma metastasize to thyroid
- Pigment, if present, is helpful
 - Melanin: Also in pigmented medullary carcinoma
- Dyscohesive cells, spindled morphology, intranuclear cytoplasmic inclusions
- **Positive:** S100 protein, HMB-45, SOX10, Melan-A, tyrosinase

Sclerosing Mucoepidermoid Carcinoma With Eosinophilia

- Epithelial islands with heavy fibrosis, mucocytes, and occasionally eosinophils
- May mimic Hodgkin lymphoma, but **positive** CD15, CD30, EBER helps with separation

STAGING

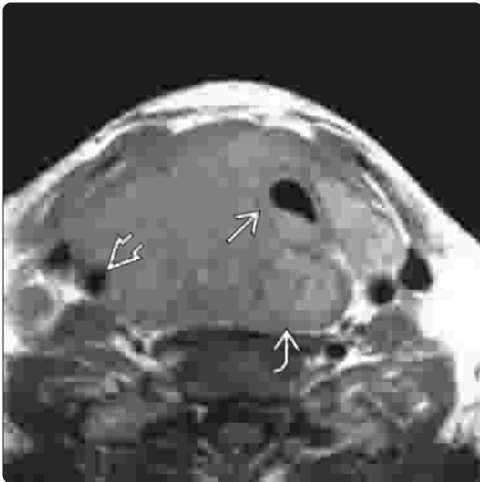
Lymphoma in General

- "E" is added because they are extranodal
 - Perithyroidal lymph nodes may be involved
 - Other lymph nodes (mediastinal, abdominal) &/or bone marrow may then be affected
 - Gastrointestinal tract, lung, bladder, and liver
- Most are IE or IIE disease at presentation
- DLBCL tend to be higher stage (IIIE or IVE)

SELECTED REFERENCES




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Large Thyroid Gland Mass Distorting Neck

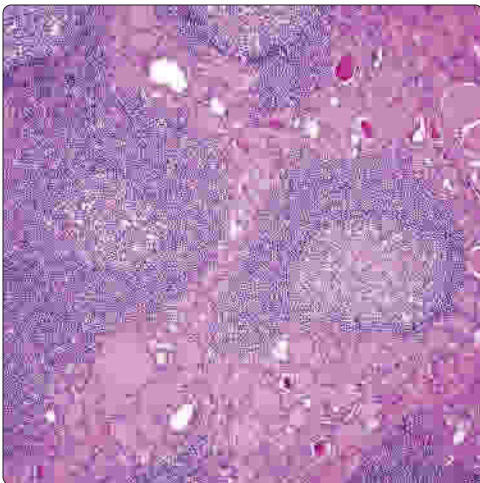


Fish Flesh Cut Appearance




(Left) Axial T1WI MR shows thyroid lymphoma as a homogeneous, circumscribed, solid thyroid mass. There is tracheal  and carotid space  displacement with concurrent invasion of the esophagus . (Right) This lobe of the thyroid gland shows a firm, slightly lobular mass, with effacement of the normal thyroid gland. The cut surface is bulging, smooth, pale-tan, and "fish flesh" with a homogeneous appearance. Extrathyroidal extension is frequently present.

Chronic Lymphocytic Thyroiditis Background

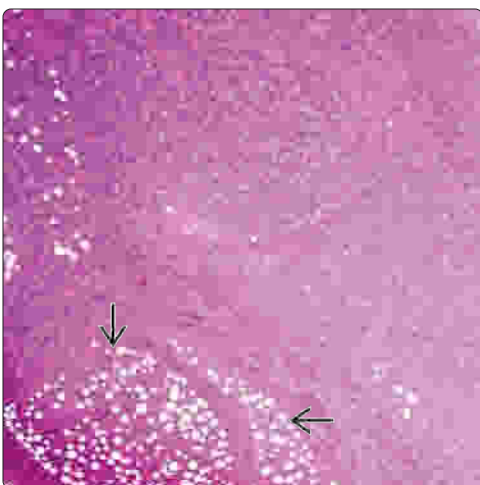


Multinodular Effacement

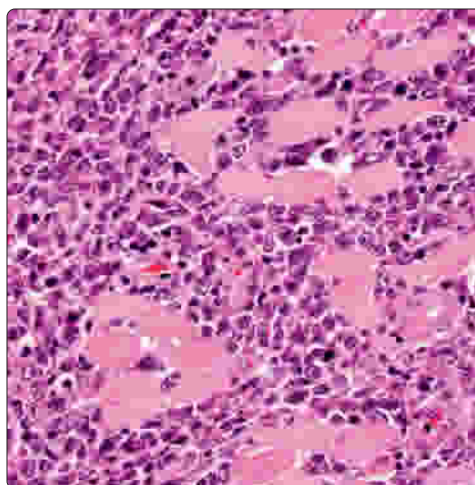



(Left) Although it may not always be identified, chronic lymphocytic thyroiditis is nearly always present in the background of all patients with primary thyroid lymphoma. In cases where it is absent, it is presumed to be overtaken by the lymphoma. (Right) A multinodular or follicular pattern is seen in this EMZBCL. Chronic lymphocytic thyroiditis is noted in the background . There are coalesced lymphoid follicles to create a more nodular appearance.

Extrathyroid Extension Into Fat



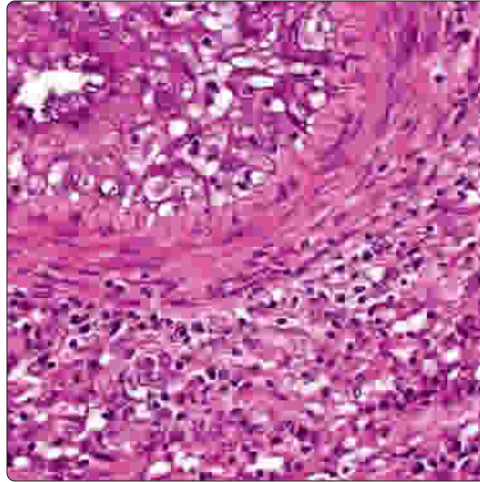
Muscle Infiltration



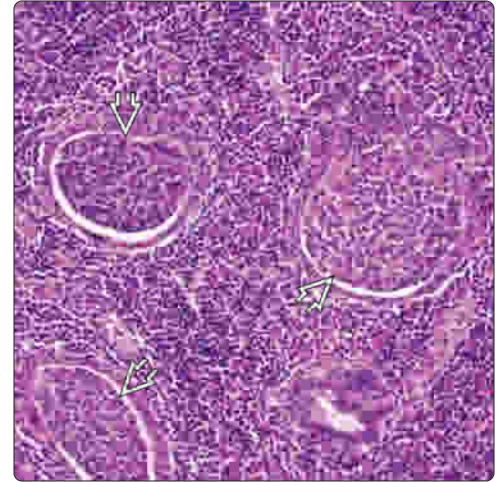
(Left) There is complete effacement of normal thyroid gland parenchyma, showing vague nodularity and diffuse patterns. There is extension of the process into the adjacent adipose tissue . (Right) The cells of a DLBCL have expanded into the perithyroidal skeletal muscle. This is a frequent finding in high-grade lymphomas. Note the plasmacytoid appearance of many of the neoplastic cells.

Angiocentric Infiltration

(Left) Atypical lymphoid cells are noted in the wall of the vessel and continuing into the subintimal space. Vascular invasion is most common in high-grade tumors, such as in this DLBCL. (Right) Lymphoepithelial lesions (LELs) are one of the best features to confirm a lymphoma. Neoplastic lymphoid cells infiltrate into and destroy the thyroid follicular epithelium. Of the 2 types, MALT balls are unique

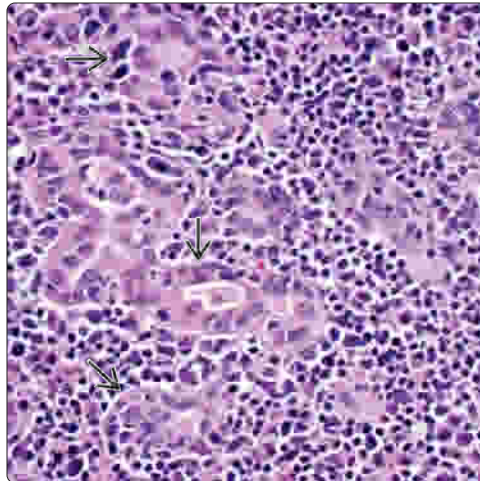


MALT Ball of Lymphoepithelial Lesion

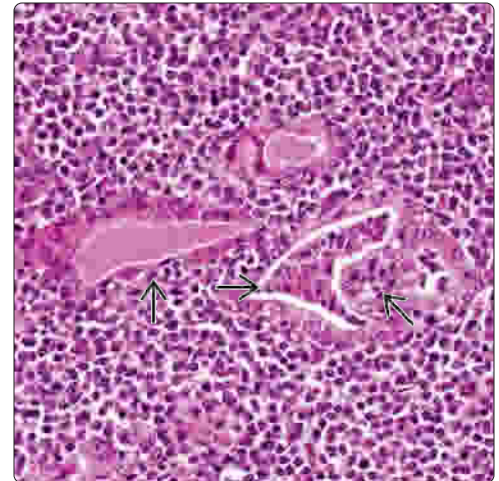


Lymphoepithelial Lesion

(Left) LELs are one of the best diagnostic features of thyroid lymphomas. They are comprised of neoplastic lymphoid cells infiltrating and destroying the thyroid follicular epithelium. (Right) LELs are neoplastic lymphoid cells that infiltrate into and destroy the thyroid follicular epithelium. Here, there are single and aggregated lymphocytes within or between the follicular epithelial cells.

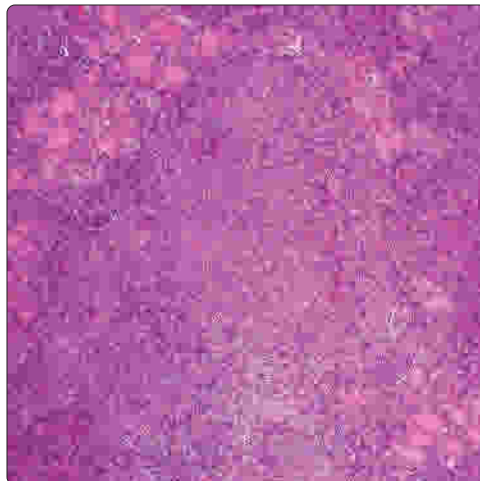


Lymphoepithelial Lesion

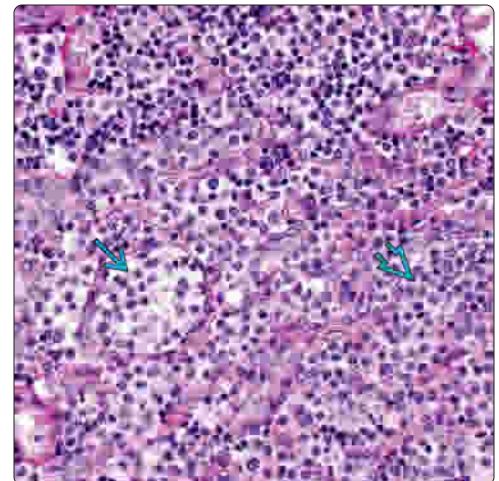


Large Follicle With Mixed Cell Population

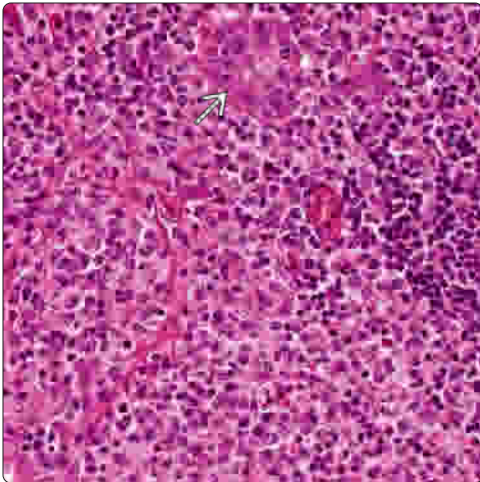
(Left) EMZBCL have a heterogeneous population of B cells, including marginal zone cells, monocytoid B cells, and plasma cells. At this low power, the expansion and enlargement of the lymphoid follicle is easy to see, with effacement of the follicles. (Right) There are atypical small lymphocytes, marginal zone (centrocyte-like) small cleaved cells, monocytoid B cells, and plasma cells. They are frequently blended with one another as in this example.



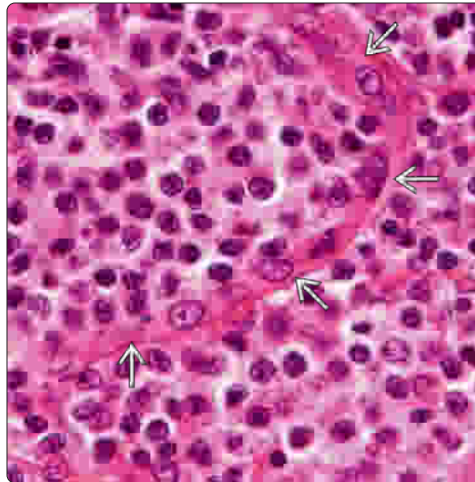
Collections of Monocytoid B Cells



Heterogenous Population of Cells

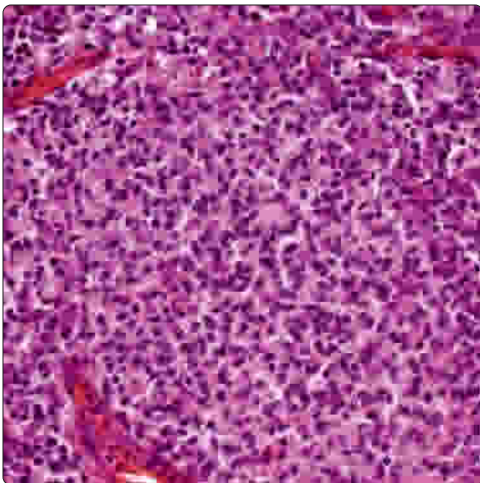


Monocytoid B Cells Within Thyroid Follicle

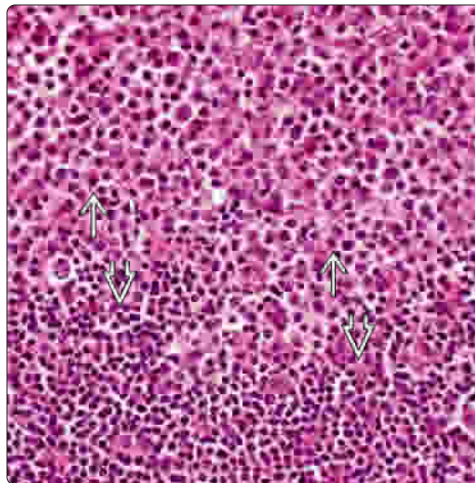


(Left) It is important to remember that EMZBCL are heterogeneous, in this field showing eosinophils, mature lymphocytes, plasma cells, and monocytoid B cells. A partially destroyed thyroid epithelial follicle is present [X]. (Right) The monocytoid B cells are a monotonous population of neoplastic lymphoid cells with abundant, pale cytoplasm with lobulated or kidney-shaped nuclei. They frequently show grooves or cleaves. They frequently aggregate, as they are within this thyroid follicle [X].

Mixture of Atypical Lymphoid Elements

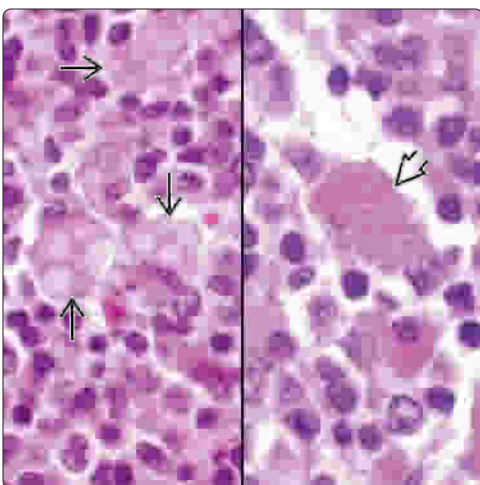


Transition From EMZBCL to DLBCL

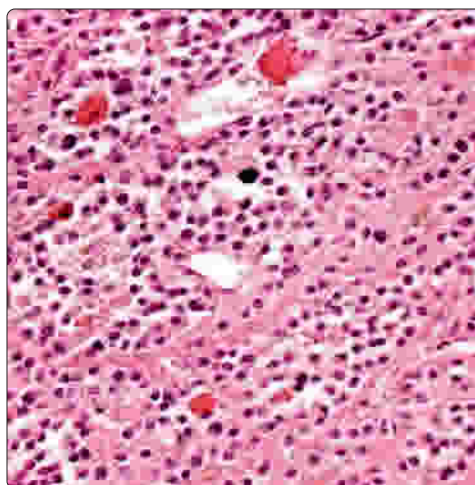


(Left) This field shows a sheet-like effacement of the thyroid epithelium, showing a population of centrocyte-like small cleaved cells and monocytoid B cells, along with a few lymphocytes in the background. (Right) There is a zone of transition from EMZBCL [X] to DLBCL [X]. It is not uncommon to see areas of transition between these 2 tumor types. Pattern of growth, atypia, and increased mitoses can help with this separation.


Mott Cells and Crystal-Storing Histiocytes



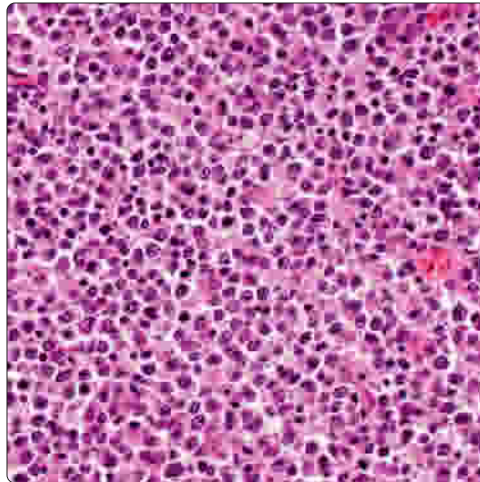
Plasmacytoid Population



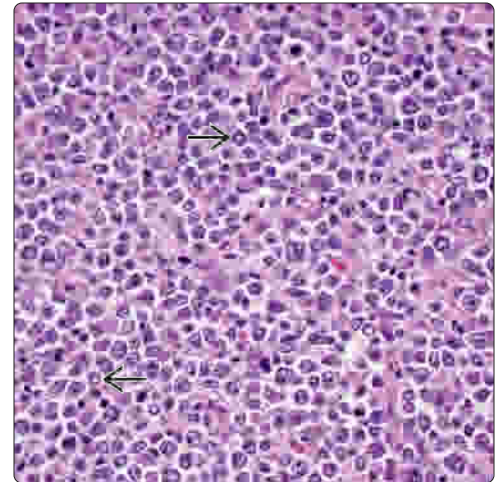
(Left) Cytoplasmic immunoglobulin (Mott cells [X]) accentuates the plasmacytoid differentiation. Uncommonly, crystal-storing histiocytes [X] may be seen. Dutcher and Russell bodies are usually easy to find. (Right) Sometimes, EMZBCL can show such extensive plasma cell differentiation (sheets of plasma cells) that it simulates a plasmacytoma. Light chain restriction demonstrates monoclonality.



(Left) In this field, there is a plasmacytoid appearance to the lymphoid population. However, it is a diffuse, sheet-like growth. There is a vaguely plasmacytoid appearance to the cells. **(Right)** Intranuclear cytoplasmic inclusions (Dutcher bodies)  can be seen in the neoplastic lymphoid and plasmacytoid cells in this EMZBCL. This abnormal immunoglobulin distribution is quite characteristic of lymphoma.

Neoplastic Plasmacytoid Population

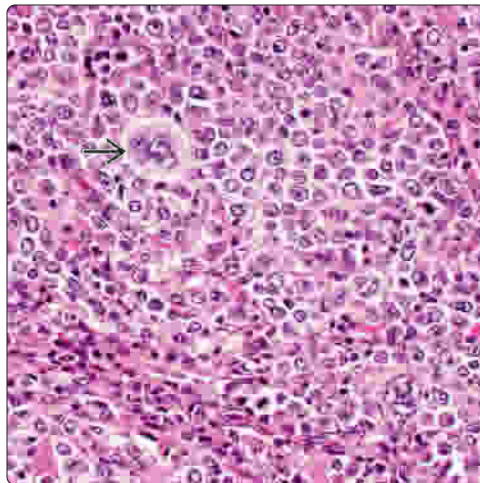


Dutcher Bodies

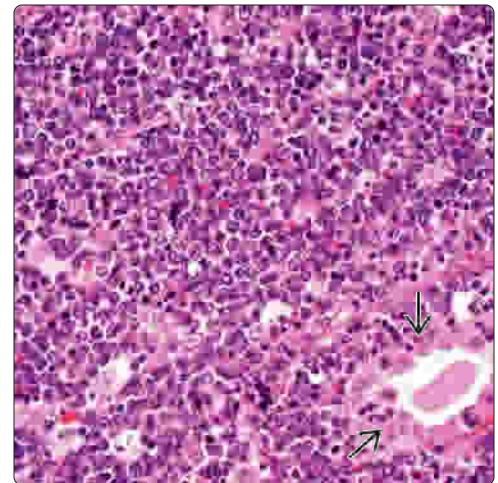



(Left) The tumor shows a sheet-like appearance of large centroblast-like cells in association with a large, multinucleated, Reed-Sternberg-like cell . These features are quite frequently present in a DLBCL. **(Right)** Occasionally the tumor is arranged in a Burkitt lymphoma-like pattern, with brisk mitotic activity, apoptosis, and a starry sky pattern. A residual thyroid follicle is present .

Reed-Sternberg-Like Cells in DLBCL

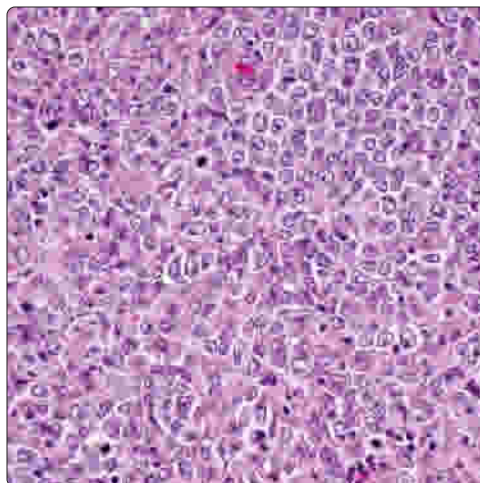


Burkitt-Like Pattern

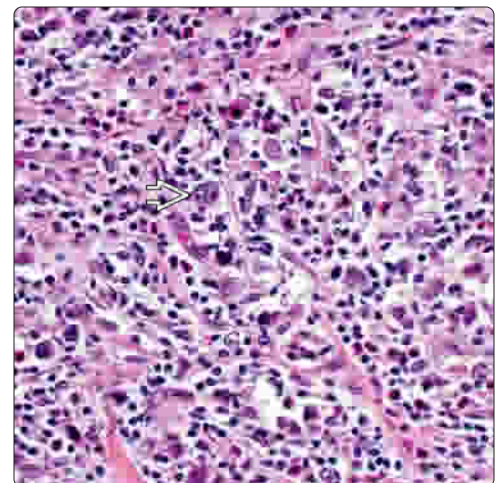


(Left) Large centroblasts are arranged in a sheet-like distribution in this example of a DLBCL. Various cell types can be seen in the tumor, with centroblasts, immunoblasts, monocytoid and plasmacytoid cells seen. **(Right)** Classical Hodgkin lymphoma, nodular sclerosis subtype is the only one identified in thyroid. Classic Hodgkin-Reed-Sternberg cells  are noted in a variably cellular background diathesis of plasma cells, eosinophils, and neutrophils. Appropriate immunohistochemistries are necessary for the diagnosis.

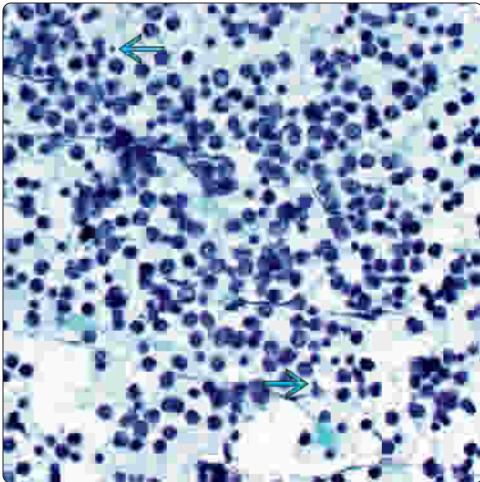
Large Cells in DLBCL



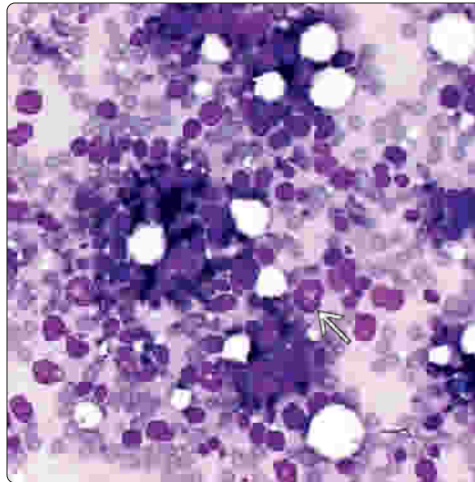
Classical Hodgkin Lymphoma



Monotonous Lymphoid Population

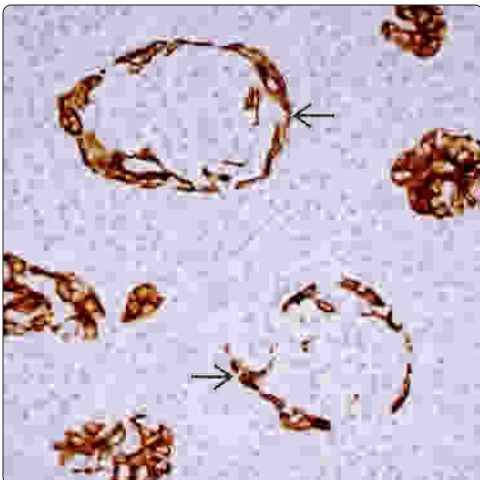


Atypical Lymphoid Cells

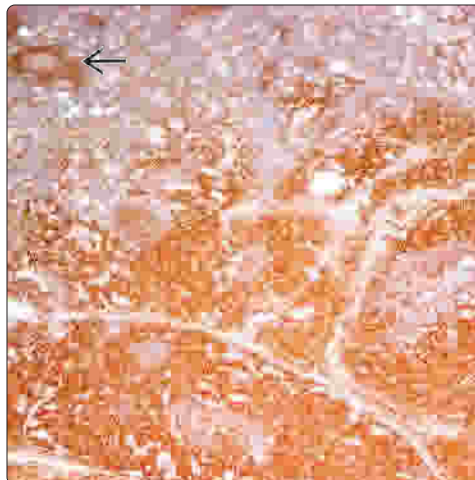


(Left) There is a cellular aspirate without thyroid follicular epithelium. The cells are monotonous, slightly enlarged, and show a background of rare lymphoglandular bodies [E]. The chromatin is slightly vesicular. This pattern can mimic a chronic lymphocytic thyroiditis. (Right) Smears show a noncohesive admixture of atypical, large (3x erythrocyte size) cells, with lymphoglandular bodies and mitotic figures [E]. Thyroid epithelium and tingible body macrophages are absent.

CK-PAN Highlights LEL

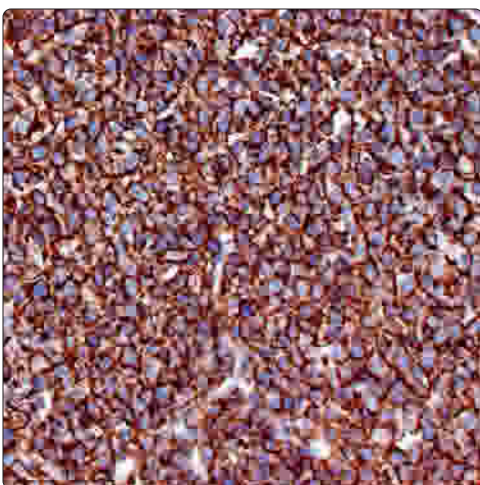


CD79a Reacts With Cells in EMZBCL

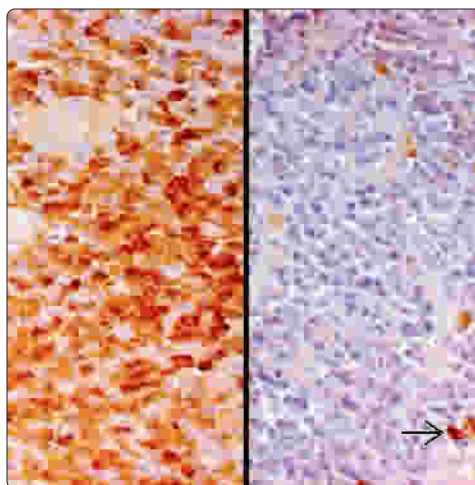


(Left) This pan-cytokeratin can be used to highlight [E] the residual thyroid follicular epithelium, especially in lymphoepithelial lesions, where atypical lymphocytes invade and destroy the follicles. (Right) Either CD79-a or CD138 can be used to highlight the plasmacytoid cells within an EMZBCL. In this case, plasmacytoid cells are also highlighted in the background germinal centers [E]. Location is important in lymphoma immunohistochemistry interpretation.

CD20 Highlights Sheet of Neoplastic Cells



Kappa Light Chain Restriction



(Left) Nearly all primary thyroid gland lymphomas are immunoreactive with CD20, giving a strong and diffuse cytoplasmic reaction in the atypical lymphocytes. By contrast, CD3 will be positive in chronic lymphocytic thyroiditis or only in isolated cells in the tumor. (Right) This EMZBCL demonstrates a remarkable restriction with κ light chain (left), while only isolated nonneoplastic cells are positive with λ light chain [E] (right).

KEY FACTS

TERMINOLOGY

- Primary thyroid gland angiosarcoma: Malignant tumor of endothelial cell differentiation

ETIOLOGY/PATHOGENESIS

- Dietary iodine deficiency, especially in alpine areas of central Europe

CLINICAL ISSUES

- Increased in inhabitants of Europe (alpine areas)
- Female >> male (4:1)
- Painless mass, often in setting of longstanding goiter
- Severe bleeding at primary or metastatic sites may complicate surgery
- Radical surgery, chemotherapy, and brachytherapy
- Overall poor prognosis; majority die in < 6 months

MACROSCOPIC

- Variegated cut surface; extensive hemorrhage and necrosis

- Tend to be large (up to 12 cm)

MICROSCOPIC

- Irregular periphery, invading thyroid parenchyma
- Tumor necrosis and hemorrhage throughout, with hemosiderin-laden macrophages
- Freely anastomosing vascular channels, with irregular, cleft-like to patulous vascular channels
- Large, epithelioid polygonal cells lining vascular channels
- Neolumen formation with erythrocytes

ANCILLARY TESTS

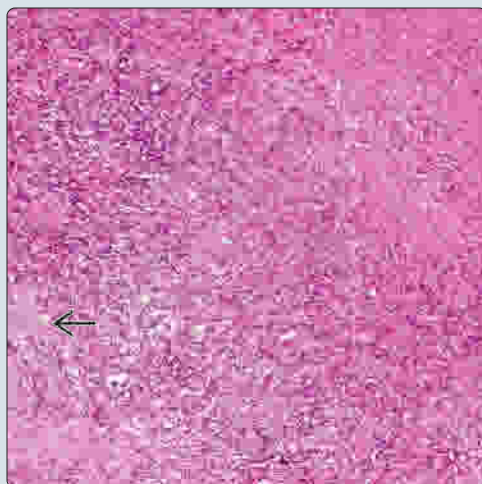
- **Positive:** CD31, FVIIIIRAg, CD34, FLI1, vimentin, and keratin
- **Negative:** TTF-1, thyroglobulin, calcitonin

TOP DIFFERENTIAL DIAGNOSES

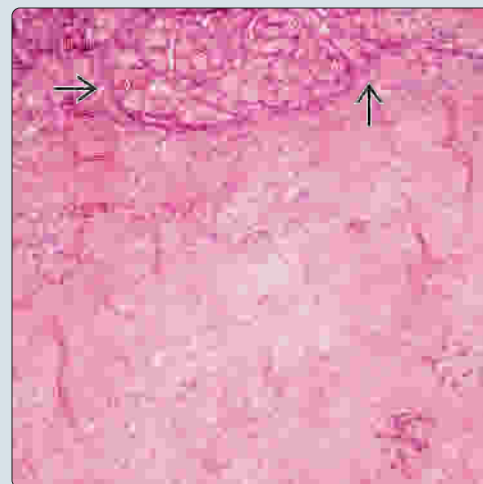
- Undifferentiated carcinoma, degenerative adenomatoid nodules, post fine-needle aspiration changes, metastatic angiosarcoma, medullary carcinoma

Infiltrating Vascular Neoplasm

(Left) There are isolated thyroid gland follicles surrounded by a vascular proliferation. There is extensive necrosis associated with the proliferation, a common finding for angiosarcoma. **(Right)** Low-power magnification shows a degenerative neoplastic proliferation immediately adjacent to and involving the thyroid gland parenchyma. Areas of necrosis are present. At this power, a vascular neoplasm may not be considered; however, extensive necrosis is present.

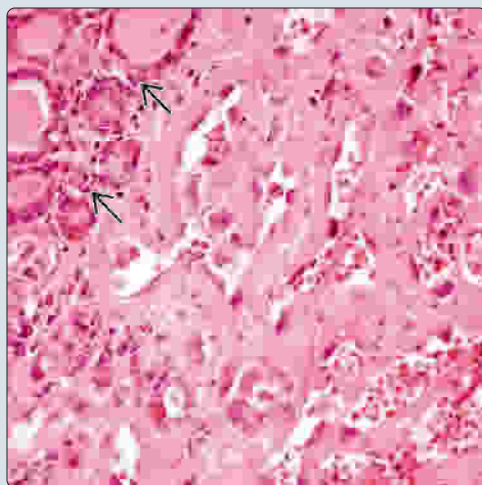


Degeneration of Angiosarcoma

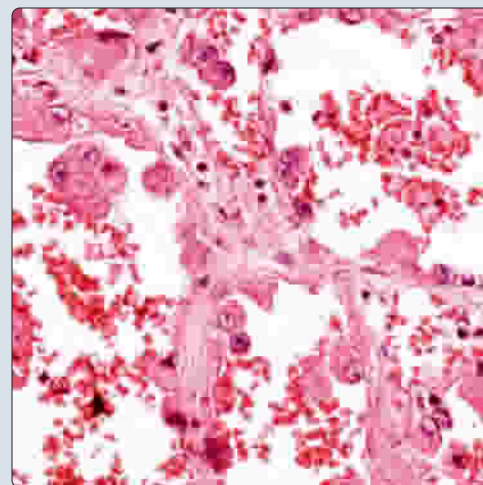


Widely Anastomosing Vascular Channels

(Left) A freely anastomosing vascular proliferation is separated by a desmoplastic stroma adjacent to thyroid follicles. Erythrocytes are noted within the channels lined by atypical endothelial cells. **(Right)** There are highly atypical endothelial cells lining these vascular channels. Note there is vacuolization of the cytoplasm. Extravasated erythrocytes are present throughout.



Atypical Endothelial Cells Line Vessels



TERMINOLOGY

Definitions

- Primary thyroid gland angiosarcoma: Malignant tumor of endothelial cell differentiation

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Dietary iodine deficiency, especially in alpine areas of central Europe
 - Prevalence reduced with iodized salt prophylaxis
- Significant occupational exposure to industrial vinyl chloride and other polymeric materials

Pathogenesis

- Endothelial origin (no thyroglobulin mRNA expression)

CLINICAL ISSUES

Epidemiology

- Incidence
 - Rare (< 2% of all thyroid gland malignancies)
 - Geographic variability is noted
- Age
 - Usually in 7th decade of life
- Sex
 - Female > > male (4:1)
- Ethnicity
 - Increased in inhabitants of central Europe (alpine areas)

Presentation

- Painless mass, often in setting of longstanding goiter
- May have dyspnea, asthenia, weight loss
- Rarely: Rapidly growing mass with pressure symptoms
- Hyperthyroidism: Angiosarcoma may have trophic effect

Treatment

- Risk of severe bleeding at primary or metastatic sites
- Radical surgery (total thyroidectomy)
- Chemotherapy can be used but may be palliative
- Adjuvant radiotherapy (brachytherapy)

Prognosis

- Overall poor prognosis
- Majority of patients die from disease (< 6 months)
- Distant metastases (lung, GI tract, bone) may cause fatal bleeding

MACROSCOPIC

General Features

- Macroscopic: Circumscribed; microscopic: Invasive
- Variegated cut surface; extensive hemorrhage and necrosis

Size

- Tend to be large; range up to 12 cm

MICROSCOPIC

Histologic Features

- Irregular periphery; blending and invasion into parenchyma
- Freely anastomosing vascular channels

- Solid, spindled, papillary, pseudoglandular
- Irregular, cleft-like to patulous vascular channels
- Tumor necrosis and hemorrhage throughout, with hemosiderin-laden macrophages
- Increased mitotic figures, including atypical forms
- Large, epithelioid polygonal cells lining vascular channels
 - Abundant eosinophilic to vacuolated cytoplasm surrounding round nuclei with vesicular chromatin
 - Prominent macronucleoli
 - Neolumen formation with erythrocytes

ANCILLARY TESTS

Cytology

- Diagnostic cytology material is difficult to interpret
- Background of necrotic material and blood
- Isolated large, epithelioid cells

Immunohistochemistry

- **Positive:** CD31, FVIIIIRAg, CD34, FLI1
 - Avoid overinterpretation of diffusion artifacts
- **Positive:** Vimentin, occasionally keratin
- **Negative:** TTF-1, thyroglobulin, calcitonin

DIFFERENTIAL DIAGNOSIS

Undifferentiated (Anaplastic) Carcinoma

- Pseudoangiomatous pattern may be seen, but solid, greater degree of pleomorphism, tumor giant cells, often with concurrent thyroid gland disease (nodules, tumor)
- Immunohistochemistry must be interpreted with caution

Degenerative Adenomatoid Nodules

- Nodules frequently undergo degenerative/retrogressive changes, with hemorrhage followed by organization
- No cytologic atypia, freely anastomosing vessels, atypical mitoses, or tumor necrosis

Post Fine-Needle Aspiration

- Common to have Masson papillary endothelial hyperplasia-type reaction
- Single site, hemosiderin-laden macrophages, extravasated erythrocytes, without atypia or anastomosing vessels

Metastatic Angiosarcoma

- Highly vascular; metastases to thyroid may be seen or direct extension (soft tissue or skin)
- Must use past history, clinical exam, radiology

Medullary Carcinoma

- Pseudoangiosarcomatous pattern may be seen, but amyloid and more characteristic areas help with diagnosis
- **Positive:** Calcitonin, synaptophysin, CEA, TTF-1

SELECTED REFERENCES

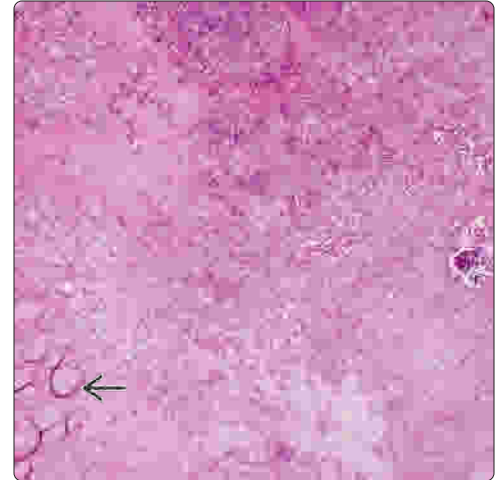
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Gross of Thyroid Angiosarcoma

(Left) Cut section of the thyroid shows areas of hemorrhage and necrosis within an encapsulated mass. (Courtesy A. Ryška, MD.) (Right) Open, freely anastomosing vascular channels can be detected in this angiosarcoma. The tumor is cellular, showing an infiltrative growth into the adjacent thyroid gland parenchyma [2]. Extravasated erythrocytes are plentiful.

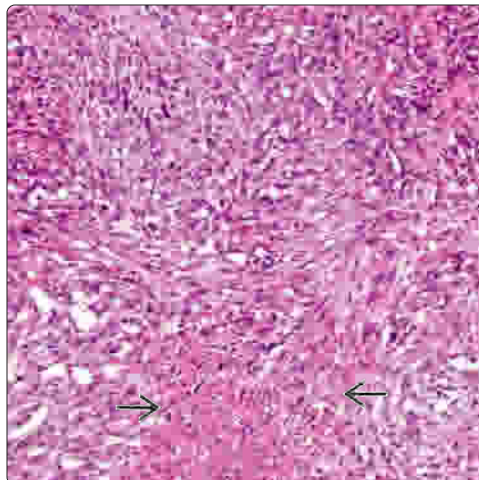


Freely Anastomosing Vascular Channels

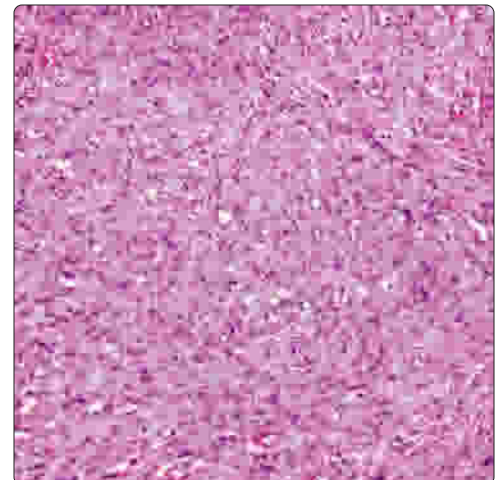


Spindled Pattern of Growth With Necrosis

(Left) Interlacing fascicles of spindled tumor cells are noted in this angiosarcoma. There is still a vascular quality with open vascular spaces and lumen formations. There is also tumor necrosis [2], a frequent finding in angiosarcoma. (Right) This tumor shows the characteristic epithelioid to spindled appearance of many primary thyroid angiosarcomas. The nuclei are vesicular and open. Thyroid parenchyma is not identified in this field. Vessels are slit-like spaces.

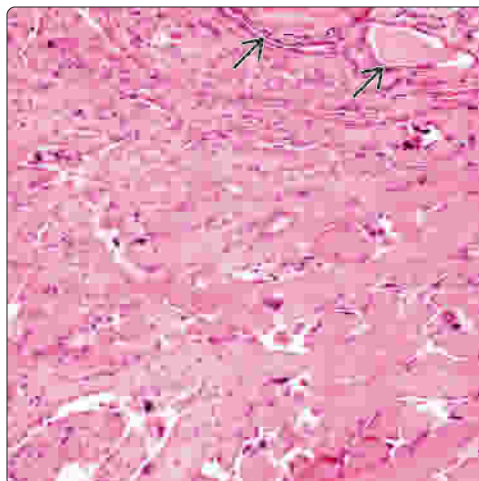


Epithelioid and Spindled Patterns

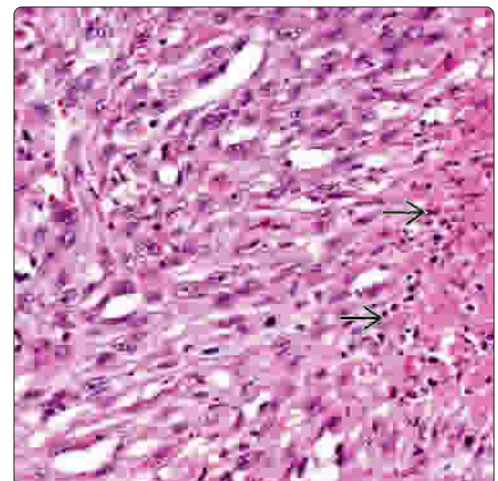


Collagenized Stroma Between Vessels

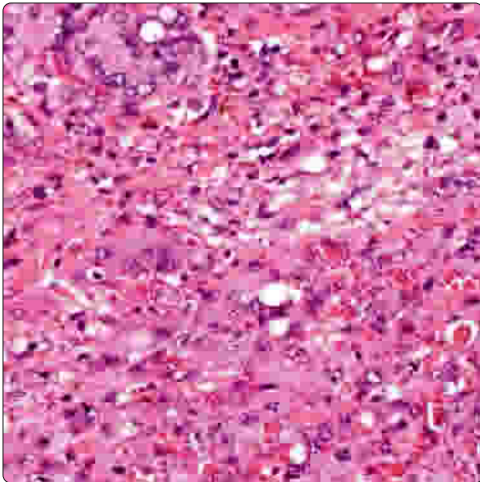
(Left) Heavy, collagenized stroma can be seen separating the tumor vessels. In this case, there are open vascular channels lined by remarkably atypical epithelioid endothelial cells. A few thyroid follicles are noted [2]. (Right) Necrosis [2] blends into the neoplastic proliferation of irregular, cleft-like vascular channels. The cells are large and epithelioid, with prominent nucleoli easily identified. Extravasated erythrocytes are easily identified throughout the lesion.



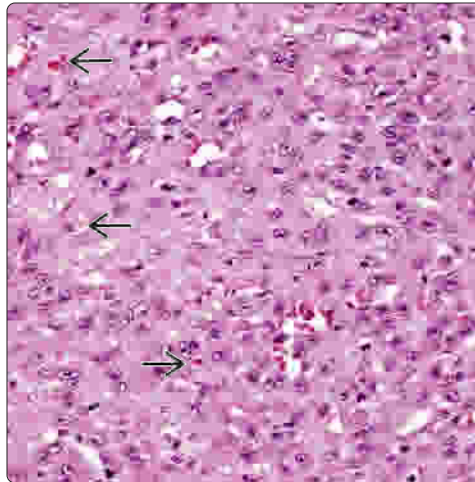
Necrosis and Cleft-Like Vascular Channels



Extravasated Erythrocytes

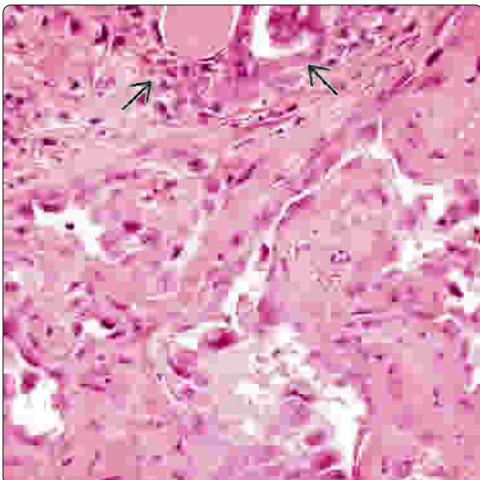


Pleomorphism With Prominent Nucleoli

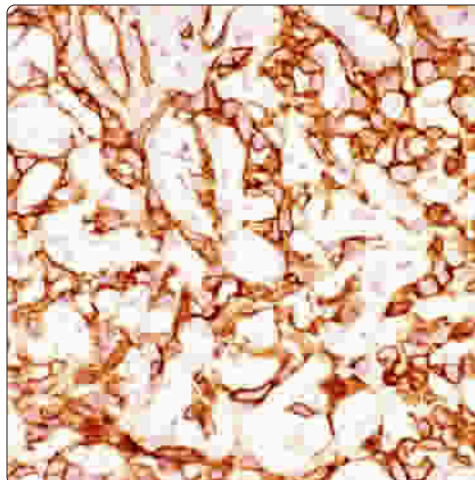


(Left) Abundant extravasated erythrocytes are present throughout this tumor. Note the vacuolization of the cytoplasm. Nucleoli are easily identified even at this intermediate magnification. The cells have a syncytial quality. (Right) Prominent macronucleoli are present within a number of epithelioid to polygonal neoplastic cells. Areas of neolumen formation [] can help to confirm the true nature of the neoplasm as an angiosarcoma. Erythrocytes are noted within the lumen.

Polygonal Endothelial Cells

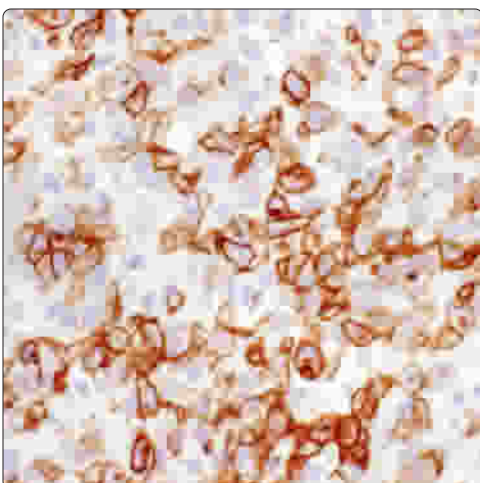


CK-PAN Stains Endothelial Cells

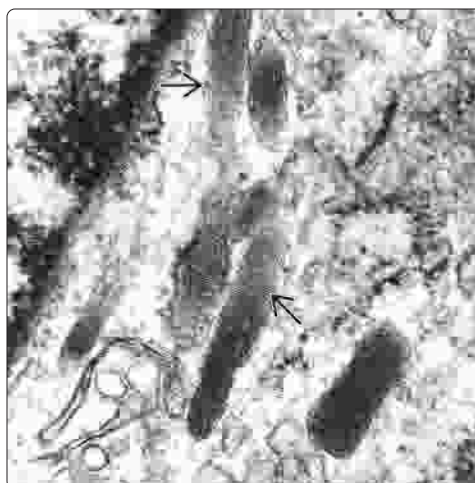


(Left) The epithelioid neoplastic cells are large and polygonal and line the patulous vascular spaces. The nuclei are vesicular. Thyroid follicular epithelium can be seen as a point of comparison []. (Right) The neoplastic endothelial cells are immunoreactive with a variety of vascular markers (CD31, CD34, FVIIIIRAg), but are also keratin immunoreactive, as seen in this thyroid angiosarcoma.

CD34 Highlights Vascular Channels



EM of Weibel-Palade Bodies



(Left) The vascular channels are highlighted by a CD34 immunohistochemistry stain. Note that the nuclei are negative, with only the cytoplasm and membrane highlighted. (Right) Weibel-Palade bodies contain fine tubules [] and are the intracytoplasmic storage granules of endothelial cells. The structures contain von Willebrand factor and P-selectin, molecules involved in homeostasis. (Courtesy S. Bhuta, MD.)

KEY FACTS

TERMINOLOGY

- Malignant primary thyroid neoplasm composed of cells with distinct smooth muscle differentiation histologically

ETIOLOGY/PATHOGENESIS

- Postulated to arise from smooth muscle-walled vessels

CLINICAL ISSUES

- Typically affects older patients
- Poor prognosis, with all patients dying from disease

MACROSCOPIC

- Nodular to bosselated outer surface, widely infiltrative periphery
- Mean: 6 cm; range: Up to 12 cm

MICROSCOPIC

- Nodular to bosselated outer surface, irregular with invasive periphery
- Entrapment and destruction of thyroid follicles

- Origin from smooth muscle-walled vessels
- Tumor necrosis usually present
- Highly cellular tumors, arranged in bundles or disordered fascicles of spindled cells
- Centrally placed, hyperchromatic, blunt-ended, cigar-shaped nuclei
 - Perinuclear cytoplasmic vacuoles quite characteristic
- Nuclear pleomorphism is pronounced
- Increased mitoses (> 5/10 HPF), including atypical forms

ANCILLARY TESTS

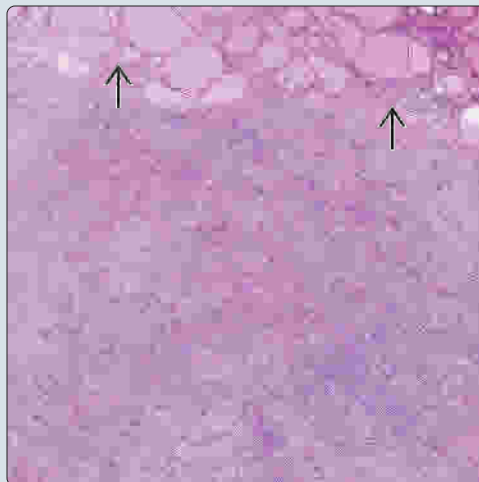
- **Positive:** SMA, MSA, desmin, caldesmon, vimentin
- **Negative:** Thyroglobulin, TTF-1, pancytokeratin, pax-8, S100 protein, chromogranin, calcitonin

TOP DIFFERENTIAL DIAGNOSES

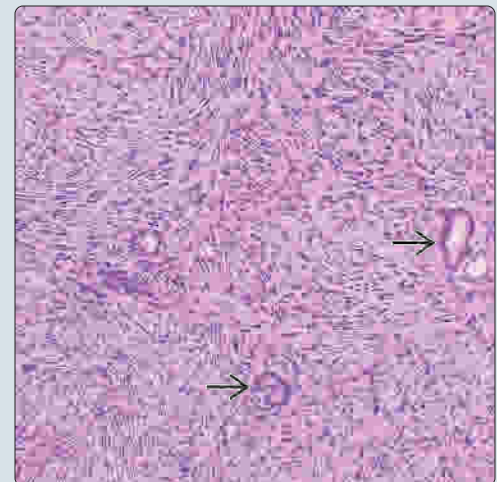
- Medullary carcinoma, undifferentiated carcinoma, metastatic leiomyosarcoma, leiomyoma, spindle epithelial tumor with thymus-like differentiation (SETTLE)

Infiltrative Spindled Cell Tumor

(Left) The thyroid gland parenchyma is compressed and pushed to the periphery by the advancing edge of this spindled cell neoplasm. From this power, a specific tumor type cannot be determined. (Right) This spindled-cell neoplastic population is noted to be entrapping and destroying the native thyroid follicles seen within the tumor. The fascicles are most suggestive of leiomyosarcoma.

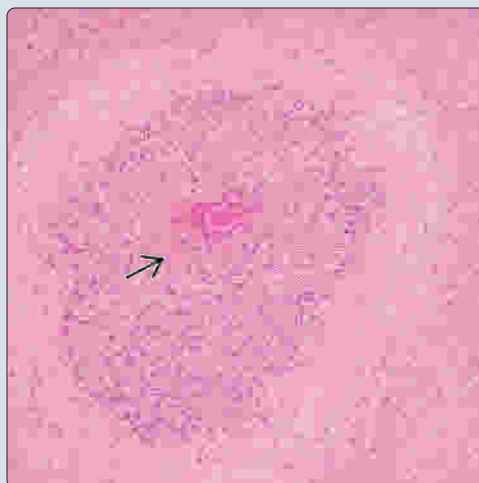


Entrapped Follicular Cells

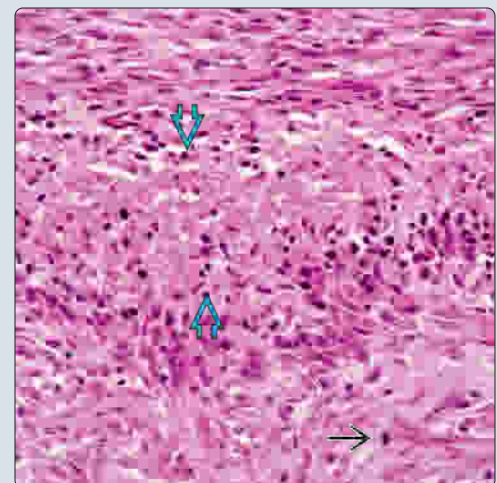


Muscle-Walled Vessel Origin

(Left) The smooth muscle wall of a large vessel is noted to blend imperceptibly with the neoplastic proliferation, a feature frequently seen in leiomyosarcoma. There is also tumor necrosis in the center of this vessel. (Right) There is a haphazard distribution of neoplastic spindled cells. The tumor cells are associated with an area of tumor necrosis. Mitotic figures are easily identified.



Tumor Necrosis in Leiomyosarcoma



TERMINOLOGY

Abbreviations

- Leiomyosarcoma (LMS)

Definitions

- Malignant primary thyroid neoplasm composed of cells with distinct smooth muscle differentiation histologically

ETIOLOGY/PATHOGENESIS

Histogenesis

- Postulated to arise from smooth muscle-walled vessels at thyroid gland periphery

CLINICAL ISSUES

Epidemiology

- Incidence
 - Exceedingly rare; < 0.02% of all thyroid gland tumors
- Age
 - Older patients
- Sex
 - Equal gender distribution

Site

- Often thyroid gland periphery

Presentation

- Nonspecific signs and symptoms, with thyroid mass, usually increasing in size
- May be associated with dyspnea, difficulty breathing, &/or stridor

Treatment

- Complete, radical surgical removal
- Adjuvant radiochemotherapy appears ineffective

Prognosis

- Poor, with all reported patients dying from disease

IMAGING

Radiographic Findings

- Inhomogeneous low-density mass in thyroid gland by CT evaluation
 - Signal intensity similar to surrounding soft tissue; possible calcifications
- Compression of upper airway, infiltration into soft tissues or cartilage, thyroid destruction, and necrosis suggestive of malignancy but not specific tumor type

MACROSCOPIC

General Features

- Nodular to bosselated outer surface, widely infiltrative periphery

Size

- Mean: 6 cm; range: Up to 12 cm

MICROSCOPIC

Histologic Features

- Irregular, invasive periphery

- Encapsulation seen but more commonly invasive
- Entrapment and destruction of thyroid follicles
- Origin from smooth muscle-walled vessels may be seen
- Vascular and perineural invasion frequently present
- Tumor necrosis usually present
- Highly cellular tumors, arranged in bundles or disordered fascicles
- Spindled tumor cells
 - Centrally placed, hyperchromatic, blunt-ended, cigar-shaped nuclei
 - Perinuclear cytoplasmic vacuoles quite characteristic
 - Nuclear pleomorphism easily identified
- Increased mitoses (> 5/10 HPF), including atypical

ANCILLARY TESTS

Immunohistochemistry

- **Positive:** SMA, MSA, desmin, caldesmon, vimentin
 - **Focal positive:** MYOD1, myogenin, CD117
- Ki-67: High labeling index
- **Negative:** Thyroglobulin, TTF-1, pancytokeratin, pax-8, S100 protein, chromogranin, calcitonin

DIFFERENTIAL DIAGNOSIS

Medullary Carcinoma

- Spindled cell morphology may be seen but with plasmacytoid appearance, "salt and pepper" nuclear chromatin, amyloid, and background C-cell hyperplasia
- **Positive:** TTF-1, calcitonin, chromogranin, CEA-M, pax-8

Undifferentiated Carcinoma

- Significant overlap clinically, radiographically, and histologically between LMS and undifferentiated carcinoma (UC)
- Longstanding thyroid disease, with recent rapid growth
- Residual thyroid carcinoma favors UC
- **Positive:** Pancytokeratin, p63; **negative:** Desmin, actins

Metastatic Leiomyosarcoma

- Direct extension and metastatic LMS to thyroid gland must be excluded by clinical or imaging correlation
 - Metastatic disease tends to be multifocal in thyroid
- Most common primary sites: Uterus, gastrointestinal tract, soft tissue

Primary Spindle Cell Tumors

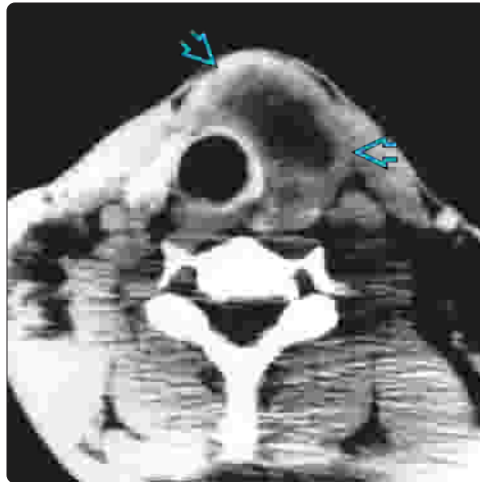
- Leiomyoma: Noninfiltrative, no pleomorphism, necrosis, or increased mitoses
- Spindle epithelial tumor with thymus-like differentiation (SETTLE): Epithelial thymus-like tumor; epithelial markers

SELECTED REFERENCES

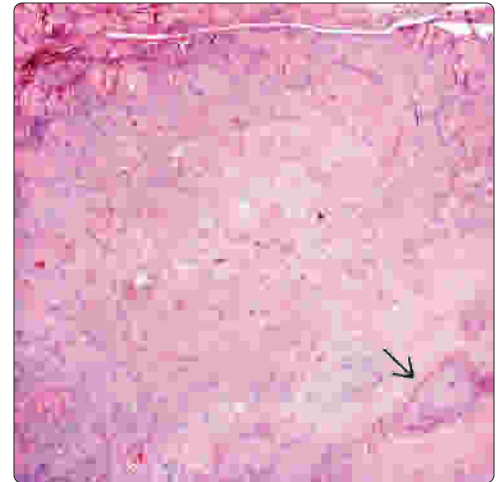
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Central Necrosis in Thyroid Mass on CT

(Left) CT scan demonstrates a large tumor replacing the left lobe of the thyroid gland [B]. There is central necrosis. Lymphadenopathy is absent. (Right) There is no encapsulation of this tumor; rather, it is an irregular invasive neoplasm. Entrapment and destruction of thyroid follicles are noted as the tumor invades. Note the large vessel [C] giving rise to the tumor.

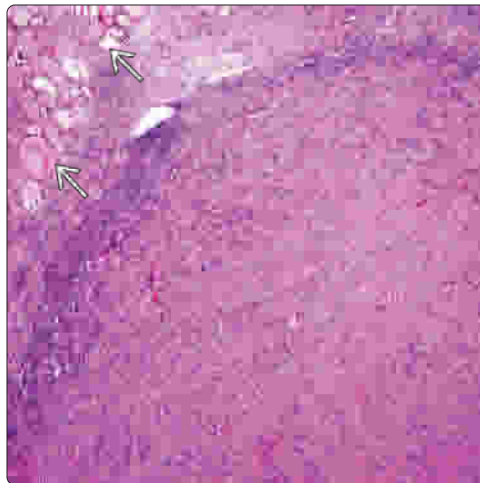


Widely Infiltrative Spindled Neoplasm

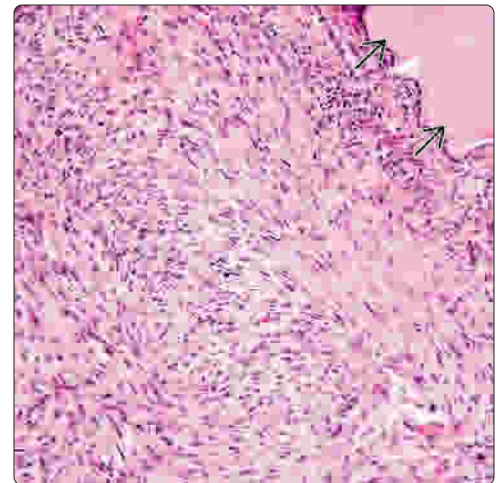


Irregular, Invasive Spindled Cell Tumor

(Left) There are a number of thyroid follicles entrapped and destroyed [B] at the periphery of the irregular, invasive neoplasm. There is no encapsulation identified. While it is a spindled cell tumor, the specific type cannot be determined from this magnification. (Right) A highly cellular neoplasm is seen, arranged in short, interlacing, disordered fascicles. The tumor cells are spindled with spindled, hyperchromatic nuclei. The thyroid follicle is entrapped at the edge [C].

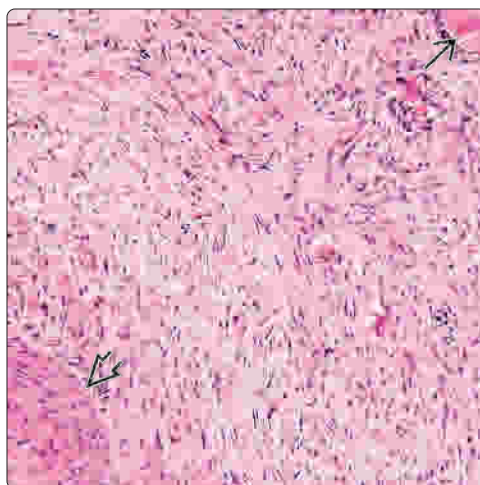


Cellular Spindled Cell Tumor

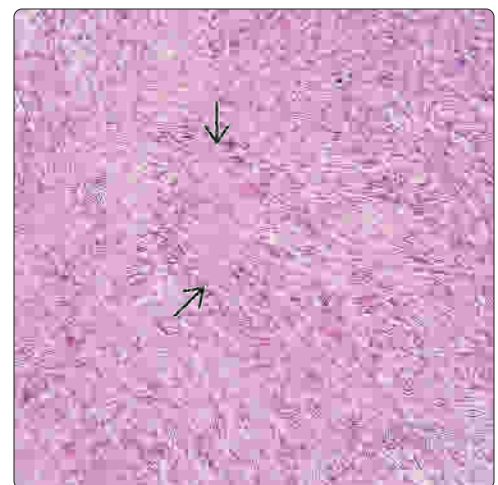


Vessel Wall Origin of Tumor

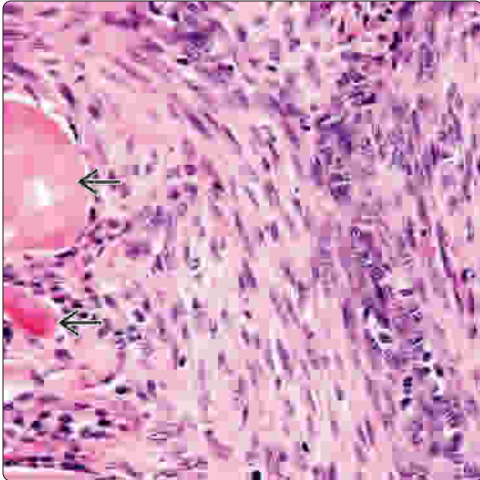
(Left) Origin from a smooth muscle-walled vessel [B] is noted in this leiomyosarcoma. The tumor cells scroll off the wall of the vessel and blend into the surrounding thyroid parenchyma [C]. (Right) Tumor necrosis is usually present [B] in a leiomyosarcoma. There is a disordered arrangement to the spindle cells, which show irregular, short bundles that intersect at acute angles. This is a characteristic pattern for leiomyosarcoma of the thyroid gland.



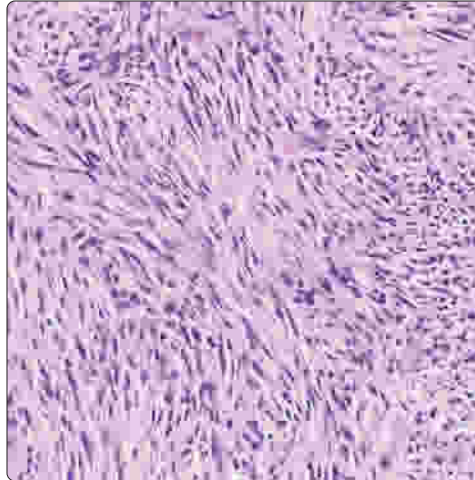
Tumor Necrosis Within Muscle Bundles



Cigar-Shaped Nuclei With Pleomorphism

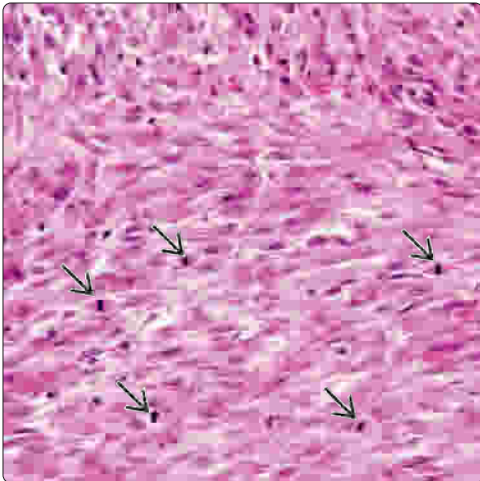


Interlacing Fascicles

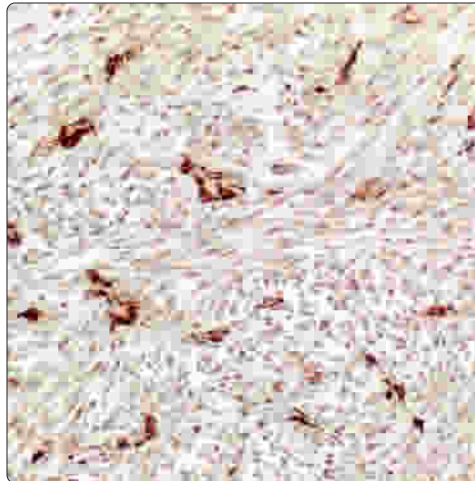


(Left) The neoplastic spindle-cell tumor shows blunt, cigar-shaped nuclei within the spindled cells. Entrapment of the thyroid follicular epithelium [] is noted. The nuclear pleomorphism is mild to moderate in this field. **(Right)** There are several, short, interlacing fascicles of neoplastic spindled cells in this leiomyosarcoma of the thyroid gland. Slightly myxoid stroma is noted in this example.

Greatly Increased Mitoses

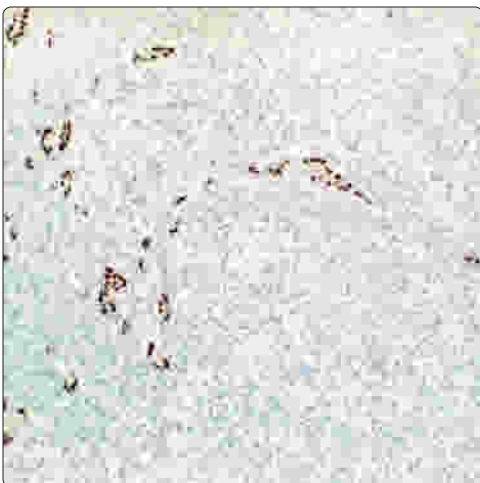


Strong, Diffuse Smooth Muscle Actin

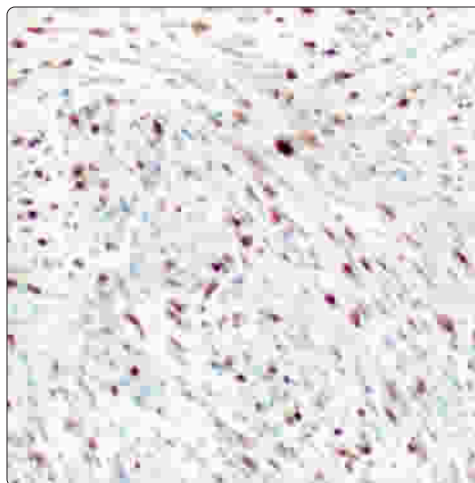


(Left) The bundles of neoplastic cells clearly demonstrate a large number of mitotic figures [], a feature that would not be seen in a benign neoplasm. Cytoplasmic perinuclear clearing is also present. **(Right)** The fascicles and bundles of neoplastic smooth muscle cells are highlighted by the smooth muscle actin. Desmin and smooth muscle myosin heavy chains would also be positive in these tumors.

Entrapped Follicles Are TTF-1(+)



High Ki-67 Labeling Index



(Left) The leiomyosarcoma cells are negative for TTF-1, whereas the entrapped and destroyed thyroid follicular epithelial cells are positive for TTF-1. **(Right)** The neoplastic cells show a very strong reaction in the nuclei with Ki-67, highlighting a greatly increased number of cells in proliferation.

KEY FACTS

TERMINOLOGY

- Malignant neoplasm composed of cells with evidence of distinct peripheral nerve sheath differentiation histologically

CLINICAL ISSUES

- May develop from medium to large nerves at periphery of gland
- Usually lobectomy or thyroidectomy, with palliative radiation
- Poor clinical outcome irrespective of clinical features, size, grade, or stage of tumor

MACROSCOPIC

- Tumors are tan to white and glistening with neural appearance
- Range: Up to 7 cm

MICROSCOPIC

- Thyroid gland infiltration, entrapment and destruction

- Arranged in tightly packed fascicles that are woven into vague herringbone pattern
- High cellularity with fusiform to spindled cells
- Fibrillar cytoplasmic extensions arranged in loose background
- Cellular pleomorphism and necrosis
- Increased mitotic figures ($> 4/10$ HPF), including atypical forms
- Tumor necrosis (comedonecrosis)

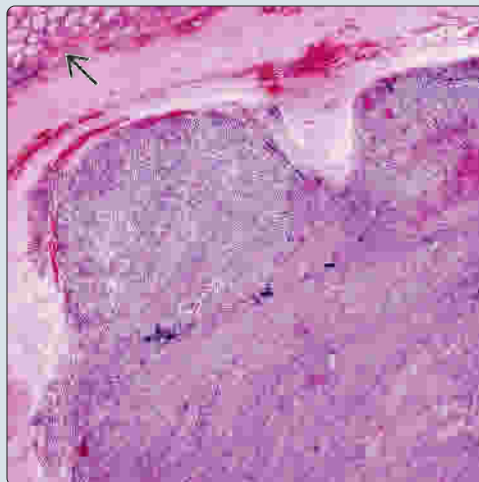
ANCILLARY TESTS

- **Positive:** S100 protein (may be focal), SOX10, vimentin, p53
- **Negative:** Thyroglobulin, TTF-1, calcitonin, actin, desmin

TOP DIFFERENTIAL DIAGNOSES

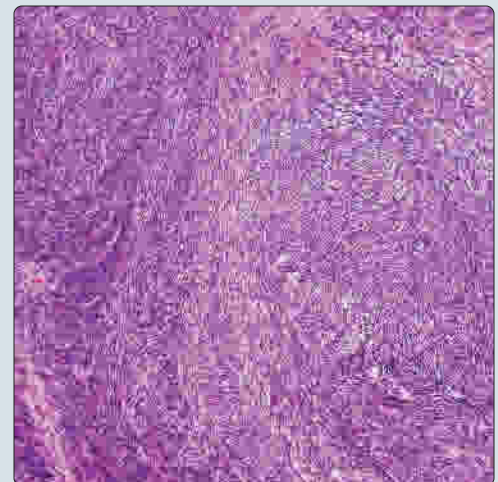
- Undifferentiated carcinoma, medullary thyroid carcinoma, Riedel thyroiditis (IgG4 sclerosing disease)
- Primary or metastatic fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, malignant fibrous histiocytoma, angiosarcoma, melanoma

Well-Encapsulated MPNST

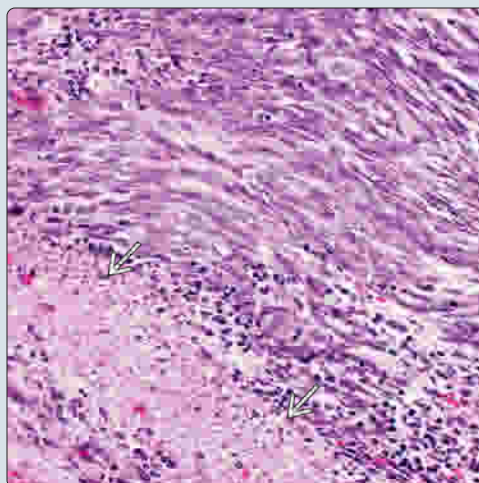


(Left) The thyroid gland parenchyma is separated from the tumor by a very thick and well-developed fibrous connective tissue capsule. The tumor is highly cellular, showing a pushing border. A vague fascicular arrangement is noted. (Right) This tumor is arranged in tightly packed fascicles that are woven into a vague herringbone pattern. There is high cellularity comprised of fusiform cells. A slightly more hypocellular area is noted.

Fascicles in Herringbone-Type Pattern

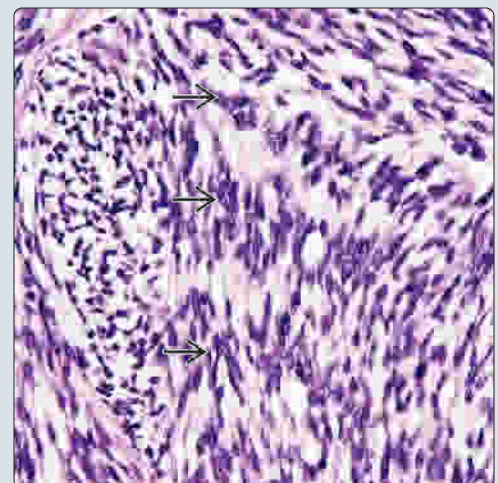


Tumor Necrosis in MPNST



(Left) This highly cellular tumor is arranged in tightly packed fascicles composed of spindled tumor cells. There is an almost syncytial quality to this tumor. Note the remarkable necrosis. Mitotic figures are increased. (Right) There is well-developed palisading in this malignant peripheral nerve sheath tumor. The spindled cells show a Verocay body-type formation. There is limited pleomorphism in this field.

Palisaded Nuclei in MPNST



TERMINOLOGY

Abbreviations

- Malignant peripheral nerve sheath tumors (MPNST)

Definitions

- Malignant neoplasm composed of cells with evidence of distinct peripheral nerve sheath differentiation histologically
 - Must arise within thyroid parenchyma or be contained within capsule of thyroid gland

ETIOLOGY/PATHOGENESIS

Histogenesis

- May arise from sympathetic and parasympathetic or possibly sensory nerves

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very rare, representing < 0.02% of all thyroid gland tumors
 - Prevalence of PNST higher among kindred with von Recklinghausen disease and neurofibromatosis
 - Although not detected in thyroid gland disease
- Age
 - All ages affected, although usually older at initial presentation
 - Syndrome-associated tumors tend to develop in patients of younger age
- Sex
 - Equal gender distribution

Site

- Although not specific site, development from medium to large nerves at periphery of gland is common

Presentation

- Signs and symptoms are nonspecific
- Thyroid gland mass, usually increasing in size
- May have associated dyspnea, difficulty breathing, and weight loss

Treatment

- Usually lobectomy or thyroidectomy
- Radiotherapy of limited palliative value

Prognosis

- Poor clinical outcome irrespective of clinical features, size, grade, or stage of tumor
 - All patients reported die from disease
- Staging is not applied, but local effects are more prognostically significant than other features

IMAGING

Radiographic Findings

- CT images show inhomogeneous, low-density mass
 - Signal density is similar to that of surrounding soft tissue
 - May show upper airway compression, infiltration into soft tissue, destruction of thyroid gland &/or necrosis
- Scintigraphic scans demonstrate cold nodule

- In general, lymphadenopathy is absent

MACROSCOPIC

General Features

- Tumors are tan to white and glistening with neural appearance
- Cut surface may focally appear cystic with yellow fluid
- Effacement of thyroid parenchyma and invasion beyond tumor capsule is common
- Tend to arise from medium to large nerves at thyroid gland periphery

Size

- Range: Up to 7 cm

MICROSCOPIC

Histologic Features

- Absence of direct extension from perithyroidal neoplasm
- Thyroid gland infiltration
 - Invasion, entrapment or destruction
- Origin from large nerves identified at thyroid gland periphery
- Vascular invasion can be seen
- Arranged in tightly packed fascicles that are woven into vague herringbone pattern
- High cellularity with fusiform cells
- Antoni B hypocellular areas can be seen
- Neoplastic cells are spindled
- Fibrillar cytoplasmic extensions arranged in loose background
- Pleomorphism usually easily identified
- Increased mitotic figures (> 4/10 HPF), including atypical forms
- Tumor necrosis (comedonecrosis)
- Hemorrhage

ANCILLARY TESTS

Cytology

- Soft tissue neck tumors may present as thyroid primary; know anatomic site
- Cellular, highly atypical spindled to epithelioid tumor cells
- Elongated, slender, and wavy nuclei
- Fibrillary metachromatic stroma (on air-dried Romanowsky-stained slides) may be present
- Necrosis and mitoses may be seen
- No colloid or thyroid follicular epithelial cells
- S100 protein may confirm neural differentiation

Immunohistochemistry

- **Positive:** S100 protein (may be focal), SOX10, vimentin, p53
- **Negative:** Thyroglobulin, TTF-1, pax-8, calcitonin, chromogranin, CD56, desmin, actins

Flow Cytometry

- Triploidy or tetraploidy associated with high-grade tumors

Genetic Testing

- Chromosome loss of 22q, monosomy 17; trisomy 7
- NF2 mutations

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
S100	Positive	Nuclear & cytoplasmic	Tends to be focal and only a limited number of cells, although strong and diffuse reactions can be seen
SOX10	Positive	Nuclear	Majority of tumor cells
Vimentin	Positive	Cytoplasmic	Nearly all tumor cells (but nonspecific reaction)
p53	Positive	Nuclear	Can be high
CK-PAN	Positive	Cytoplasmic	Only in rare and isolated tumor cells, in limited number of cases
Thyroglobulin	Negative		
TTF-1	Negative		
Calcitonin	Negative		
Actin-sm	Negative		
Desmin	Negative		
STAT6	Negative		

Electron Microscopy

- Narrow to broad, entangled cell processes
- Processes covered by discrete basement membrane substance
- Fibrous long-spacing collagen, with its distinct periodicity
- Cytoplasmic intermediate filaments
- Primitive cellular junctions
- Collagen fibers are banded together and inserted into basal lamina

DIFFERENTIAL DIAGNOSIS

Undifferentiated (Anaplastic) Carcinoma

- Spindle cell type specifically
- Based purely on treatment and prognosis considerations, separation from primary MPNST is not clinically significant
- Often associated with preexisting thyroid disease
- Often lacks all thyroid and epithelial markers but also lacks neural markers
 - MPNST must have definite evidence of specific Schwann cell derivation histologically, immunophenotypically, &/or ultrastructurally

Sarcomas

- Both primary and metastatic sarcomas must be excluded
- Malignant triton tumor (malignant schwannoma with rhabdomyoblastic differentiation) is vanishingly rare
- Fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, malignant fibrous histiocytoma, or angiosarcoma
 - Direct extension from soft tissue primary
 - Metastatic disease from distant primary
 - Primary thyroid gland tumor
- Each tumor usually has specific growth pattern and distinctive immunohistochemical features

Medullary Thyroid Carcinoma

- Spindle cell variant specifically
- Usually has plasmacytoid cells, spindled cells, salt and pepper nuclear chromatin pattern, and amyloid
- **Positive:** Calcitonin, chromogranin, CEA, TTF-1

Riedel Thyroiditis (IgG4 Sclerosing Disease)

- Fibrosis, focally storiform, with dense lymphoplasmacytic infiltrate and obliterative phlebitis
- IgG4(+) plasma cells > 50/HPF, and IgG4/IgG ratio of > 40%

Spindle Cell Melanoma (Metastatic)

- Metastatic spindle cell melanoma is also S100 protein and SOX10 positive
- **Positive:** HMB-45, Melan-A, and tyrosinase reactions would help to separate from MPNST

GRADING

Not Used

- While not used, features include
 - Nuclear anaplasia, increased mitoses (> 4/10 HPF), tumor comedonecrosis, vascular invasion

STAGING

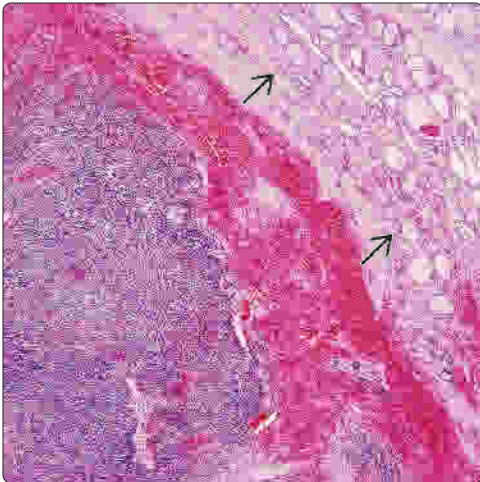
Not Used

- Although not approved, staging as undifferentiated carcinoma may be meaningful in management

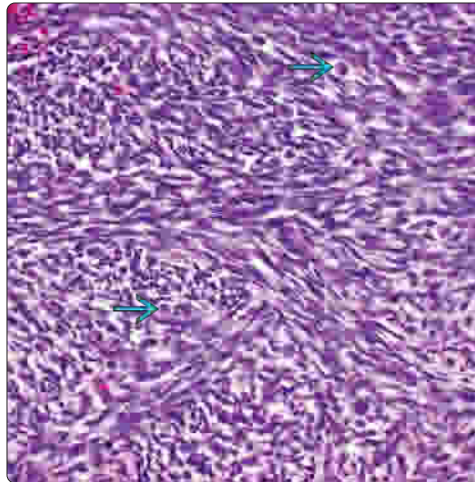
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Pushing Border With Thyroid Gland

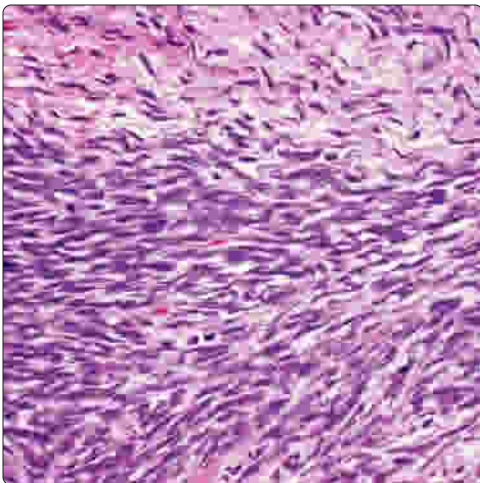


Interlacing Fascicles

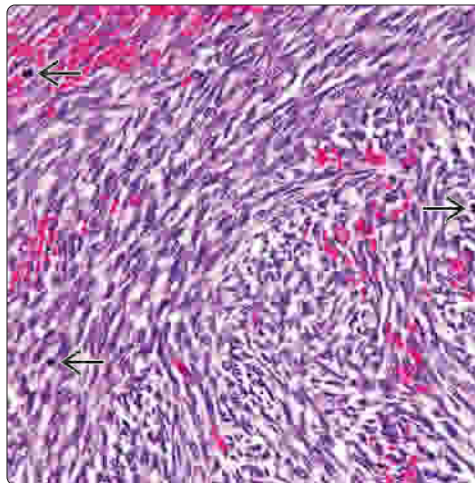


(Left) The tumor abuts the thyroid gland parenchyma. Hemorrhage is noted at the leading edge of this tumor. The neoplasm is quite cellular, although a specific histology cannot be determined from this low power. (Right) The tumor is highly cellular, with the neoplastic spindled cells arranged in tight interlacing fascicles or herringbone appearance. Mast cells are seen.

Fibrillary Cytoplasm of Spindled Cells

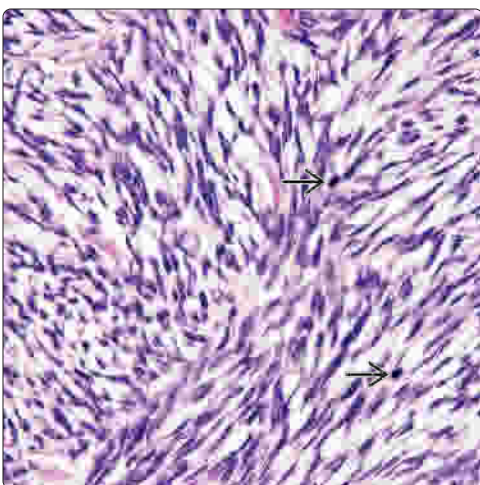


Highly Cellular Tumor With Mitoses

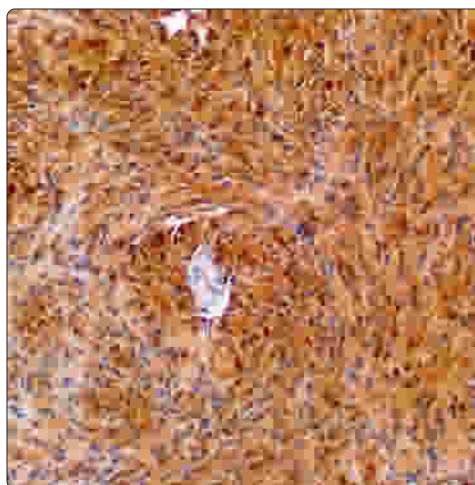


(Left) The tumor cells are arranged in a tightly packed fascicle, composed of fusiform to spindled cells. At the periphery, the fibrillar cytoplasmic extensions arranged in a loose background are more easily identified. There is cytologic atypia, although it is not well developed. (Right) This is a highly cellular tumor, showing compact spindled cells arranged in interlacing fascicles. There is mild pleomorphism. There is no cytoplasmic vacuolization. Increased mitoses are noted.

Cytoplasmic Clearing



Strong, Diffuse S100 Protein Reactivity



(Left) Malignant peripheral nerve sheath tumors are often arranged in tight fascicles. The neoplastic cells are spindled with clear cytoplasm, allowing the tapering nuclei to be seen. Mitoses are noted. (Right) It is unusual to have a malignant peripheral nerve sheath tumor show such strong and diffuse nuclear and cytoplasmic reactivity with S100 protein; however, this particular area was identified in a tumor that otherwise showed only focal immunoreactivity.

KEY FACTS

TERMINOLOGY

- Primary thyroid gland neoplasm composed of follicular dendritic cells
- Follicular dendritic cells are antigen-presenting cells, identified in primary and secondary germinal centers

CLINICAL ISSUES

- Cervical lymph nodes may show alterations of hyaline vascular-type Castleman disease
- Rarity makes predictions about prognosis difficult, but ~ 80% 5-year survival

MICROSCOPIC

- Well circumscribed, solid, tan-gray
- Invades into and blends with thyroid gland parenchyma
- Lymphatic and blood vessel invasion is common
- Arranged in diffuse, fascicular, and whorled patterns
- Syncytial arrangement of spindled to epithelioid cells

- Ample eosinophilic cytoplasm surrounds round to spindled nuclei
- Nuclear chromatin is open (vesicular)
- Mitoses are usually easily identified, sometimes increased

ANCILLARY TESTS

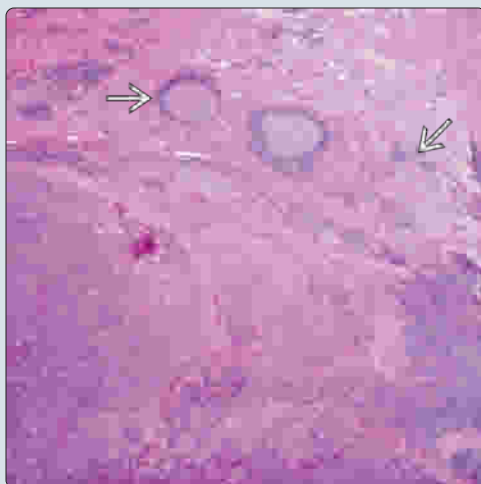
- Lesional cells **positive**: CD21, CD23, CD35, fascin, CXCL13, clusterin, EGFR, vimentin
- *BRAF*V600E mutations identified in ~ 18% of follicular dendritic cell tumors

TOP DIFFERENTIAL DIAGNOSES

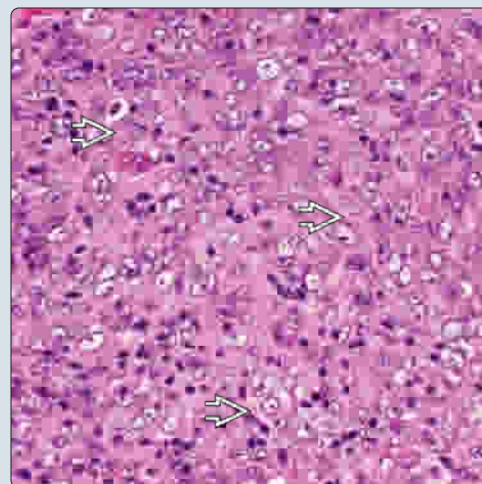
- Undifferentiated carcinoma & medullary thyroid carcinoma
- Langerhans cell histiocytosis & diffuse large B-cell lymphoma
- Leiomyosarcoma & malignant peripheral nerve sheath tumor
- Carcinoma showing thymus-like differentiation (CASTLE) and spindle epithelial tumor with thymus-like differentiation (SETTLE)

Intrathyroid Spindled Proliferation

(Left) In this focus, the chronic lymphocytic thyroiditis is quite prominent at the leading edge of the tumor ➡. The neoplasm is unencapsulated, arranged in a lobular to sheet-like distribution. (Right) There is a suggestion of epithelioid growth in this tumor. Note the cell borders ➡ that hint at squamoid differentiation. The nuclei, however, are vesicular with prominent nucleoli. There are inflammatory elements throughout.



Sheet-Like Epithelioid Growth

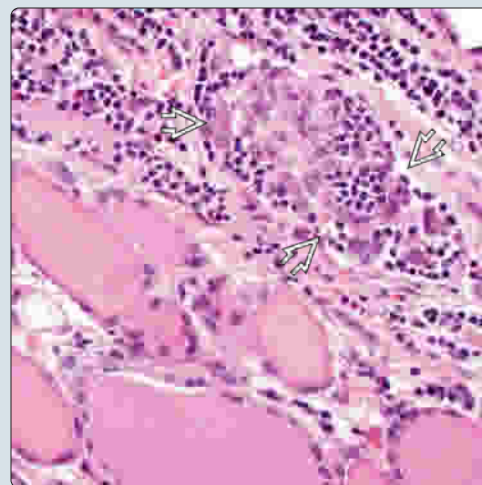


Entrapped Thyroid Follicular Epithelium

(Left) Thyroid follicles ➡ are entrapped by the neoplastic proliferation. The tumor is arranged in a diffuse sheet, lacking any specific architecture. (Right) The thyroid gland follicles are unremarkable, although associated with a chronic inflammatory infiltrate. Note the tumor thrombus filling a lymphatic space ➡. It is very common to see lymphatic or vascular space invasion in follicular dendritic cell (FDC) tumors.



Tumor Thrombus in Lymphatic



TERMINOLOGY

Abbreviations

- Follicular dendritic cell (FDC) tumor

Synonyms

- Follicular dendritic cell sarcoma (FDCS)
- Reticulum cell sarcoma

Definitions

- Primary thyroid gland neoplasm composed of follicular dendritic cells

ETIOLOGY/PATHOGENESIS

Etiology

- Possible association with hyaline vascular-type Castleman disease (may be variant histology)
- Environmental exposure rarely reported

Histogenesis

- Follicular dendritic cells are antigen-presenting cells, identified in primary and secondary germinal centers
- Putative cell of origin for follicular dendritic cell tumor

CLINICAL ISSUES

Epidemiology

- Incidence
 - Very rare; more common in Waldeyer ring (oropharynx) and cervical lymph nodes
- Age
 - Develops in older patients (60 years), rare in pediatrics
- Sex
 - Equal gender distribution

Presentation

- Present with slowly growing painless mass
- Cervical lymph nodes may show alterations of hyaline vascular-type Castleman disease (up to 20%)
- Regional lymph nodes positive in up to 50%
- Rare paraneoplastic pemphigus association (autoimmune bullous disease, severe stomatitis, polymorphous skin eruptions, and underlying neoplasms)

Treatment

- Complete surgical excision, with combination chemotherapy &/or radiation

Prognosis

- Rarity makes predictions about prognosis difficult (~ 80% 5-year survival)
- Recurrence and metastases frequent
 - 13% lymph node metastases; 13% distant metastases (lung, liver, adrenal, bone)
- Secondary thyroid involvement may also be seen

MACROSCOPIC

General Features

- Well circumscribed, solid, tan-gray
- In larger tumors, necrosis and hemorrhage may be seen

Size

- Large variation in size (1-21 cm)

MICROSCOPIC

Histologic Features

- Tumors are unencapsulated
- Invades into and blends with thyroid gland parenchyma
- Lymphatic and blood vessel invasion is common
- Tumors are cellular
- Arranged in diffuse, fascicular, and whorled patterns
- Syncytial arrangement of spindled to epithelioid cells
 - Ample eosinophilic cytoplasm surrounds round to spindled nuclei
 - Oval or elongated nuclei with open, vesicular, finely dispersed chromatin and delicate membranes
 - Small, well-defined nucleoli
 - Nuclear pseudoinclusions are common
- Mitoses are usually easily identified, sometimes increased
- Uncommonly, grape-like clusters of nuclei create giant cells, resembling Warthin-Finkeldey cells
- Lymphocytes are seen within tumor
 - Perivascular lymphoid cuffing may be seen
- Chronic lymphocytic thyroiditis often present
- Coexistent changes of hyaline-vascular Castleman disease may be seen
 - Regressed (involved) germinal centers with hyalinization, thick blood vessel walls, and interfollicular vascular proliferation
- Rarely, inflammatory pseudotumor-like variant may be seen
 - Admixture of lymphocytes, plasma cells, and histiocytes with remarkable fibroblastic reaction, with hemorrhage and necrosis; fibrinoid deposits in blood vessel walls
- Rarely, high-grade transformation may be seen
 - Significant pleomorphism, high mitotic count (> 30/10 HPF), and coagulative necrosis

ANCILLARY TESTS

Immunohistochemistry

- Lesional cells strongly positive with CD21, CD23, CD35, fascin, CXCL13, clusterin, EGFR, vimentin

Genetic Testing

- *BRAF*V600E mutations identified in ~ 18% of FDC tumors

DIFFERENTIAL DIAGNOSIS

Undifferentiated Carcinoma

- Spindled cell morphology may be seen in undifferentiated carcinoma, but there are usually areas of definitive epithelial differentiation
- **Positive:** Epithelial markers, but TTF-1 and thyroglobulin frequently negative

Medullary Thyroid Carcinoma

- Tumor spindling may be seen, and may be dominant finding; tends not to have lymphoid or histiocytic elements
- **Positive:** Calcitonin, synaptophysin, CEA-M and pancytokeratins

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
CD21	Positive	Cytoplasmic	Nearly all tumor cells; weak-patchy staining of thyroid follicular epithelium may be seen as background staining
CD23	Positive	Cytoplasmic	Nearly all tumor cells; lymphoid germinal centers will be highlighted as internal control
CD35	Positive	Cytoplasmic	Most tumor cells
Fascin	Positive	Cytoplasmic	Most tumor cells
CXCL13	Positive	Dot positivity	Cytoplasmic and dot positivity
Clusterin	Positive	Cytoplasmic	Most tumor cells
Vimentin	Positive	Cytoplasmic	Nearly all tumor cells
Synuclein	Positive	Cytoplasmic	γ-Synuclein is strongly positive (reactive or neoplastic cells)
CD68	Positive	Cytoplasmic	Variably present
EMA	Positive	Cytoplasmic	Variably present
S100	Positive	Nuclear & cytoplasmic	Variably present, but usually limited
CD45RB	Positive	Cytoplasmic	Only isolated cells
CD20	Positive	Cytoplasmic	Only isolated cells
EBV-LMP	Negative		
CK-PAN	Negative		
CK8/18/CAM5.2	Negative		

Langerhans Cell Histiocytosis

- Langerhans cells are oval to polygonal with grooved, folded, indented nuclei, mixed with eosinophils
- **Positive:** CD1a, CD207 (langerin), S100 protein

Diffuse Large B-Cell Lymphoma

- Rarely may be spindled, but B-cell phenotype or molecular studies will make separation

Leiomyosarcoma

- Rare primary malignancy, often seen arising from smooth muscle vessels
- **Positive:** SMA, MSA, desmin

Malignant Peripheral Nerve Sheath Tumor

- Rare primary malignancy, arranged in spindled cell morphology, tapering nuclei
- **Positive:** SOX10, S100 protein

Carcinoma Showing Thymus-Like Differentiation (CASTLE)

- Rare epithelial malignancy, with sheets of epithelium separated by desmoplastic stroma; squamoid and syncytial architecture with lymphocytes
- **Positive:** Pancytokeratin, p63, pax-8, CD5, CD117

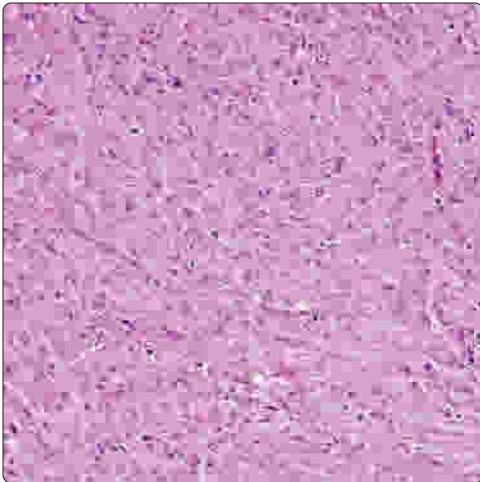
Spindle Epithelial Tumor With Thymus-Like Differentiation (SETTLE)

- Biphasic tumor with short, interlacing and streaming tight fascicles blended with tubulopapillary and glandular structures
- **Positive:** AE1/AE3, EMA, CK7

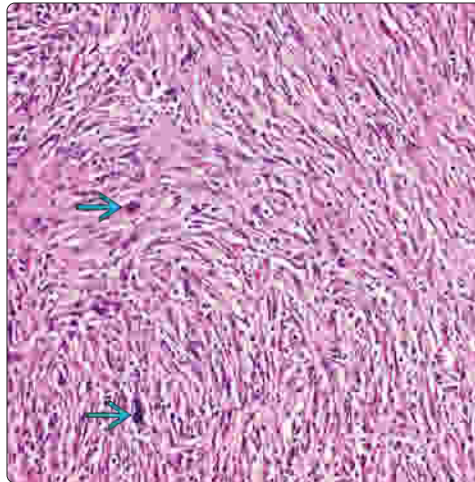
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Sheet-Like to Syncytial Architecture

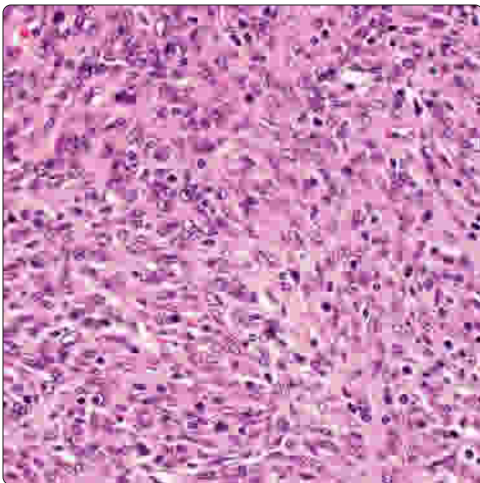


Storiform Pattern of Growth

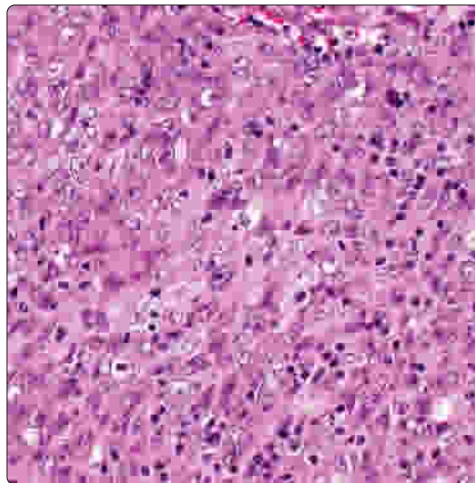


(Left) The tumor has a sheet-like pattern of growth, giving a diffuse appearance. The neoplastic cells are slightly spindled, with a vaguely syncytial architecture. (Right) A storiform-type architecture can sometimes be seen, with the neoplastic cells separated by delicate collagen. There are numerous lymphocytes sprinkled throughout the tumor, and isolated tumor giant cells [box] in this lesion.

Poorly Differentiated Tumor Cells

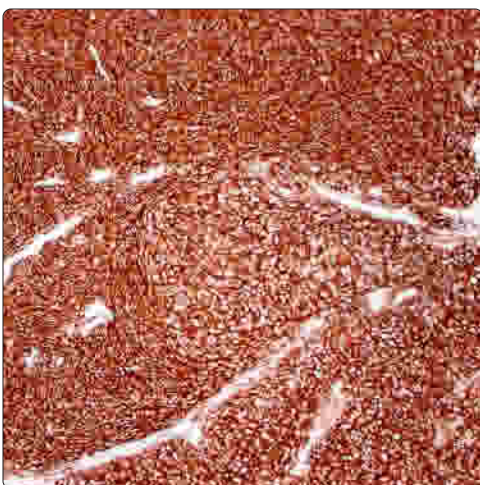


Vesicular Open Nuclear Chromatin

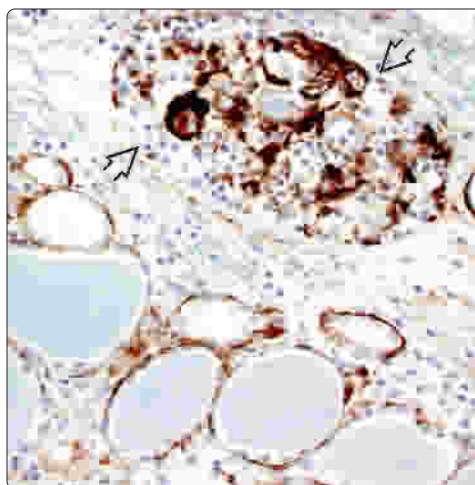


(Left) The high cellularity, with poorly differentiated tumor cells and inflammatory elements, may mimic undifferentiated carcinoma. It is in cases like this that immunohistochemistry becomes useful. (Right) The sheet-like growth of epithelioid cells intimately associated with lymphocytes gives an appearance similar to metastatic lymphoepithelial carcinoma. Note the prominent nucleoli within vesicular nuclei.

Strong and Diffuse CD23 Reaction



Intravascular CD21 Positive Reaction



(Left) There is a diffuse, sheet-like, strong membrane immunoreactivity with CD23. A similar reactivity can be seen with CD35 in FDC tumors. Similar reactivity can be found in the germinal centers of lymphocytic thyroiditis, although highlighting only the follicular dendritic cells. (Right) The neoplastic cells within the vascular space are strongly and diffusely highlighted with CD21 [box]. Note the background staining of the thyroid follicles.

KEY FACTS

TERMINOLOGY

- Tumors secondarily involving thyroid gland as result of hematogenous/lymphatic spread from primary malignancies of distant sites

CLINICAL ISSUES

- Mean age: 62 years
- Female > male (1.2:1)
- Thyroid is richly vascularized, predisposing to relatively high frequency of metastases
 - Predilection for larger vessels at thyroid periphery
- Mean interval to diagnosis of metastasis from primary tumor: 70 months
- Thyroid metastases are initial manifestation of occult primary in up to 40%
- Underlying thyroid disease results in clinical presentation in most patients
- Usually multifocal and bilateral

MICROSCOPIC

- Usually similar to primary tumor
- Distinctly different architecture and histology from primary thyroid neoplasms
- Presents as small deposits within lymph/vascular spaces or as solitary mass
- Interlobar fibrous septations widened, with tumor filling lymphatic channels
 - Predilection for larger vessels at thyroid periphery
- Carcinomas are most common (~ 80%)

ANCILLARY TESTS

- Metastatic tumors have unique immunohistochemical profiles, distinctly different from thyroid primaries

TOP DIFFERENTIAL DIAGNOSES

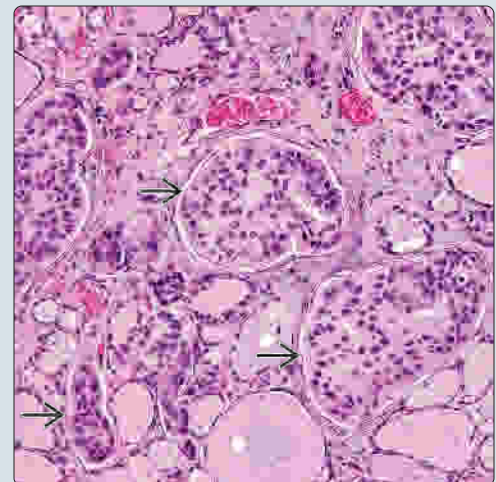
- Follicular adenoma/carcinoma, metastatic tumors to primary neoplasms, direct extension, medullary carcinoma

Metastatic Renal Cell Carcinoma

(Left) Metastatic renal cell carcinoma (RCC) frequently presents as a solitary nodule or mass. There is a well-defined capsule surrounding this tumor mass. The tumor is composed of clear cells with extravasated erythrocytes. **(Right)** Metastatic breast carcinoma is most frequently identified within lymphatics. The cells can be quite variable, showing glandular profiles. H&E alone may not allow separation from other adenocarcinomas.

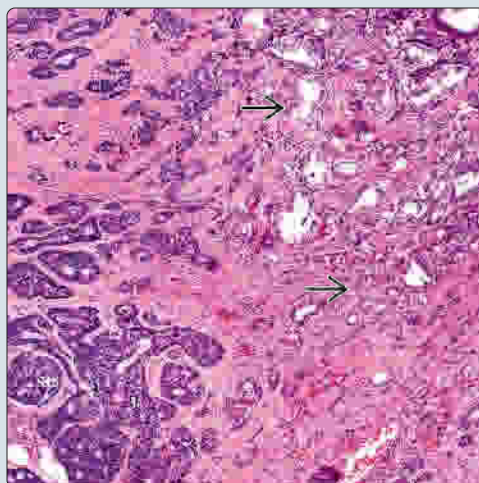


Breast Carcinoma Within Lymphatics

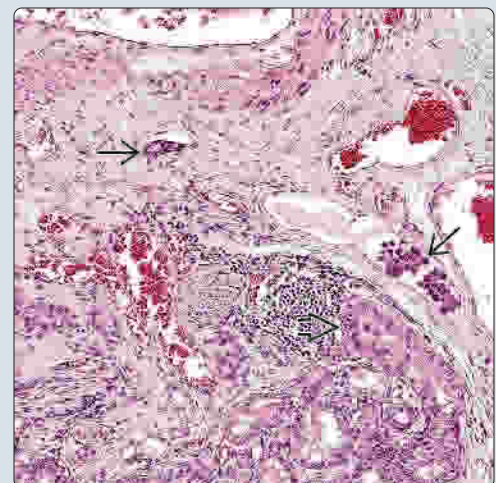


Tumor-to-Tumor Metastasis

(Left) This is an example of a metastatic adenoid cystic carcinoma (parotid gland) to a thyroid papillary carcinoma. Papillary carcinoma is the most common primary thyroid tumor type affected by metastases. Note the blending. **(Right)** The lymphatic channels at the periphery of the thyroid gland show a metastatic papillary adenocarcinoma, proven to be from a lung primary. Note the thyroid papillary carcinoma concurrently present in the extrathyroidal soft tissues (including nerves).



Metastatic Lung Adenocarcinoma



TERMINOLOGY**Synonyms**

- Renal cell carcinoma (RCC); squamous cell carcinoma (SCC)

Definitions

- Tumors secondarily involving thyroid gland as result of hematogenous/lymphatic spread from primary malignancies of distant sites
 - Direct extension from contiguous structures is excluded

ETIOLOGY/PATHOGENESIS**Pathogenesis**

- Thyroid gland is richly vascularized, predisposing to relatively high frequency of metastases
- Abnormal thyroid tissue (adenomatoid nodules, thyroiditis, neoplasms) contains metastases more frequently than normal tissue
 - Alterations in vascularity or blood flow may contribute to development of metastatic disease

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Depends on underlying frequency of primary tumor
 - Surgical series: 0.4-1.4% of removed thyroid glands
 - Potential increased incidence related to
 - Advances in radiographic techniques
 - Improved treatments, resulting in prolonged survival
 - Increased frequency of fine-needle aspiration (FNA)
 - Up to 25% in autopsied patients with disseminated malignancies
- Age
 - All ages affected; mean: 62 years
- Sex
 - Female > male (1.2:1)

Site

- Majority present with unilateral involvement (80%)

Presentation

- Underlying thyroid disease results in clinical presentation in most patients
- Patients present with thyroid gland mass
 - Occasionally, rapidly enlarging thyroid mass
- Hoarseness, dysphagia, dysphonia, neck pain, hemoptysis uncommonly identified
- Hyperthyroidism due to thyroid parenchymal destruction and hormone release
- Thyroid gland metastases are initial manifestation of occult primary in up to 40% of patients
 - Most frequently noted in RCC
- Mean interval to diagnosis of a metastasis from primary tumor: 70 months
 - 20% are synchronous
 - RCC tends to have long latency period (up to 22 years)
- Primary site depends on age and gender
 - Carcinomas are most common but sarcomas also reported

Treatment

- Surgical approaches
 - Specific procedure dictated by primary thyroid disease (in most cases)
 - Surgery advocated if tumor is slow growing or it is isolated metastasis

Prognosis

- Usually poor clinical outcome, determined by primary type; although, exceptions occur
 - Metastasis to thyroid gland correlates with poor prognosis
 - If metastatic disease is limited to thyroid, surgery can result in prolonged survival (especially for RCC)

IMAGING**Radiographic Findings**

- US: Multiple, ill-defined, infiltrating, hypoechoic nodules with heterogeneous texture without microcalcifications

MACROSCOPIC**General Features**

- Usually multifocal and bilateral
 - Surgical series: Unilateral solitary mass more likely
 - RCC is most common tumor with unilateral, solitary mass
- May metastasize to preexisting thyroid lesions

Size

- Wide range: up to 15 cm (50% are macroscopic)

MICROSCOPIC**Histologic Features**

- Usually resemble primary tumor; although, dedifferentiation can occur
- Fibrous septa within gland are frequently widened, with tumor filling lymphatic channels
- Carcinomas are most common (~ 80%)
 - Leiomyosarcoma and skin melanoma are most common noncarcinomas
- Separated into 2 forms
 - Small deposits within lymph-vascular spaces
 - Peripheral lymph-vascular channels show tumor most frequently
 - Solitary mass
- Distinctly different architecture and histology
 - Primary lung adenocarcinomas
 - Glands, large cells, high nuclear:cytoplasmic (N:C) ratio, coarse chromatin, prominent nucleoli
 - Metastatic clear cell RCC
 - Polygonal cells with clear cytoplasm, distinct cell membranes, small nuclei
 - Rich vascular network, pseudoalveolar pattern, extravasated erythrocytes filling spaces
 - Metastatic neuroendocrine carcinomas mainly in septa
- Sarcomas can be primary or metastatic
 - Leiomyosarcoma, angiosarcoma, malignant peripheral nerve sheath tumors
 - Clinical, radiographic, histologic, and immunohistochemical features used in aggregate

Primary Sites Metastatic to Thyroid Gland

Primary Site	Approximate Frequency
Kidney (renal cell carcinoma)	40%
Lung (squamous cell, adenocarcinoma, neuroendocrine)	15%
Breast	14%
Gastrointestinal tract	14%
Esophagus (squamous cell, adenocarcinoma)	4%
Stomach	4%
Colon	3%
Skin (melanoma usually)	4%
Uterus (leiomyosarcoma, cervix squamous cell carcinoma)	3%
Miscellaneous (including sarcomas)	10%

Based on review of ~ 514 cases reported in medical literature (1965-2014).

- Metastases to thyroid primary tumors are uncommon

ANCILLARY TESTS

Cytology

- Clinical and radiographic findings, cytology, and immunohistochemistry combined to yield diagnosis
 - FNA is of lesser utility if primary tumor is occult
 - **Tumor-to-tumor** metastasis is much more difficult due to 2 lesions being present
- FNA or core needle biopsy is initial study of choice: Confirms malignancy but is frequently misinterpreted as to type
- Smears are cellular, often showing 2 distinct cell populations
 - One is uninvolved thyroid gland parenchyma
 - Other is metastatic neoplastic population
- RC has bloody background, lacks colloid, and shows stripped nuclei or rare cells with clear cytoplasm
- Adenocarcinoma: Gland formation, well-developed cell borders, and coarse, heavy nuclear chromatin with prominent nucleoli
- Metastatic poorly differentiated carcinoma can mimic primary undifferentiated thyroid carcinoma

Immunohistochemistry

- Metastatic tumors may have unique immunohistochemical profile, with notable exceptions
 - Lung adenocarcinoma: **Positive:** TTF-1, CEA-M, CK7; **negative:** Thyroglobulin
 - Small cell carcinoma: **Positive:** Chromogranin, synaptophysin, TTF-1; **negative:** Calcitonin, CEA-M
 - Renal cell carcinoma: **Positive:** pax-8, CA9, RCC; **negative:** TTF-1, thyroglobulin
- Thyroglobulin may diffuse into adjacent tissue or be entrapped within metastatic deposits

Genetic Testing

- Helpful, although there are overlapping results
 - **BRAF:** Identified in papillary thyroid carcinoma, melanoma, colorectal carcinoma, ovarian carcinoma
 - **KRAS:** Codon 12/13 mutations much more likely in lung, colon, and other sites than thyroid primaries

DIFFERENTIAL DIAGNOSIS

Follicular Adenoma/Carcinoma

- Specifically, clear cell adenoma and carcinoma
- Single, unilateral mass with well-defined capsule and easily identified colloid
- Lacks prominent vascularity and extravasated erythrocytes
- **Positive:** TTF-1, thyroglobulin, pax-8

Metastatic Tumors to Primary Neoplasms

- Both tumors are concurrently present, usually interspersed, but occasionally as single tumor deposit

Medullary Carcinoma

- Solitary, solid mass, often with background of C-cell hyperplasia, generally lacking prominent interstitial disease
- **Positive:** Calcitonin, CEA-M, chromogranin, synaptophysin, TTF-1

Direct Extension

- Direct extension from adjacent organs usually radiographically and clinically distinctive

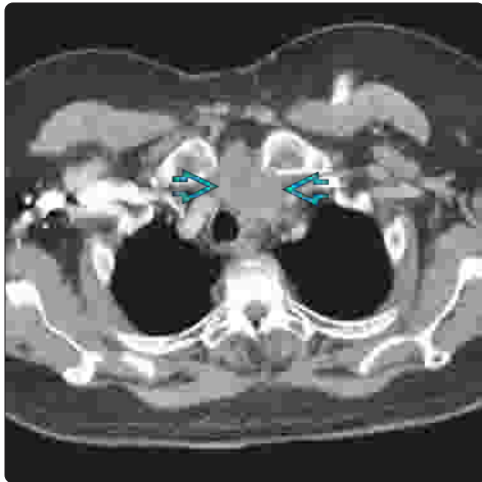
Parathyroid Carcinoma

- Tends to have well-defined cell borders, cleared cytoplasm, nuclear pleomorphism
- **Positive:** Chromogranin, synaptophysin, parathyroid hormone; **negative:** Parafibromin, TTF-1, thyroglobulin

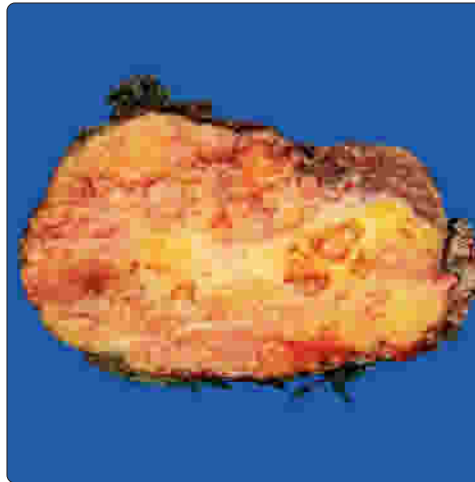
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3. Chung AY et al: Metastases to the thyroid: a review of the literature from the last decade. *Thyroid.* 22(3):258-68, 2012
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5. Heffess CS et al: Metastatic renal cell carcinoma to the thyroid gland: a clinicopathologic study of 36 cases. *Cancer.* 95(9):1869-78, 2002

Mediastinal Thyroid With Metastasis

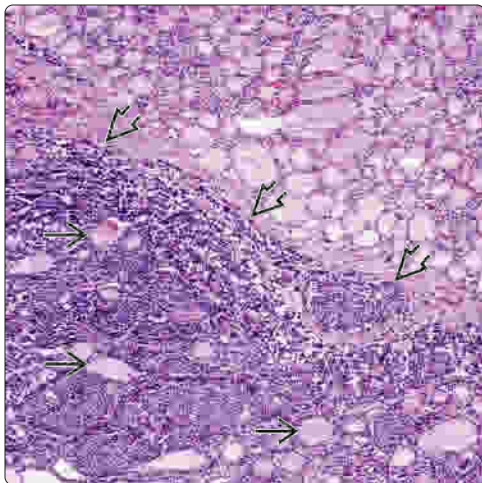


Fleshy Tumor Mass

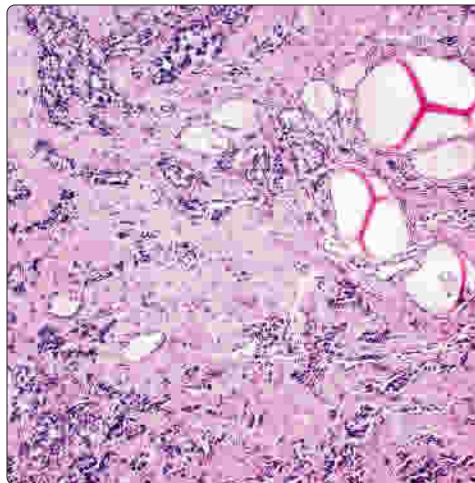


(Left) The radiographic findings are often difficult to interpret. In this case, there is enlargement of the thyroid gland, with a mass identified within a mediastinal extension of the enlarged gland [5]. This was an example of metastatic urothelial carcinoma to thyroid. (Right) The thyroid lobe has a fleshy appearance, with multiple nodules and areas of degeneration. No well-defined masses are identified. The histology showed a metastatic lung adenocarcinoma.

Metastatic Breast Ductal Carcinoma

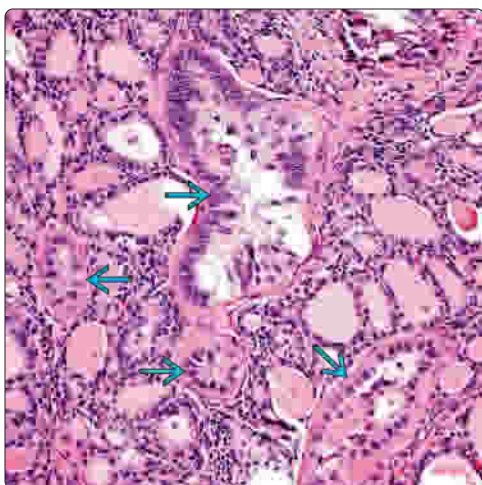


Widened Fibrous Septa

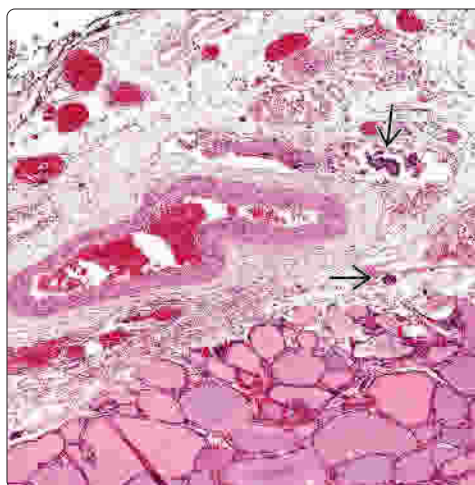


(Left) There is a mass [5] appearance to this metastatic breast ductal carcinoma. Note the entrapped thyroid epithelium [5], an important consideration when interpreting follow-up immunohistochemistry. (Right) The fibrous septa of the thyroid gland are widened, with the tumor cells filling the lymphatic spaces. This creates a sclerotic appearance to this metastatic lung adenocarcinoma. This may mimic a primary papillary carcinoma.

Lymphatics Filled With Metastatic Tumor



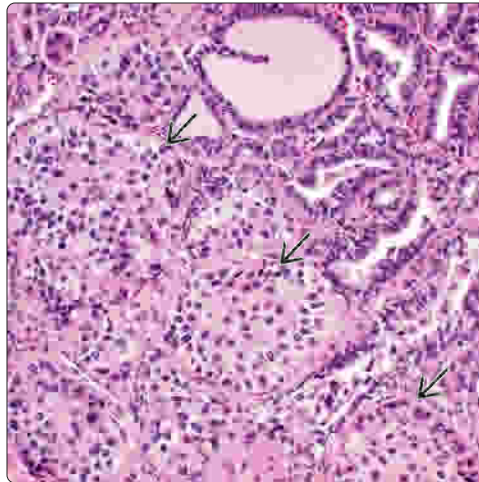
Papillary Tumor Within Lymphatics



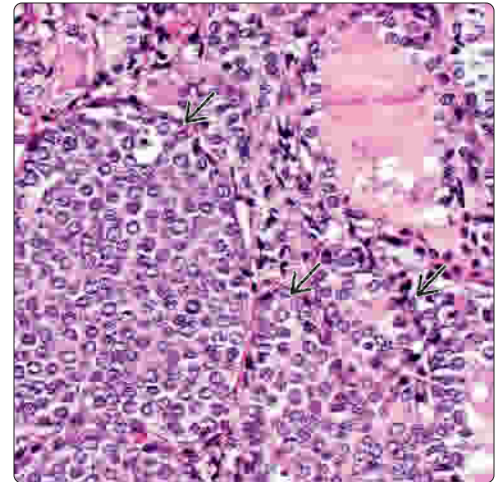
(Left) Metastatic adenocarcinoma is confined to the lymphatic spaces [5], but the widened lymphatic spaces separate between the residual thyroid follicles. At low power, this often creates a cellular appearance to the thyroid gland. (Right) The ideal location to look for a metastatic tumor is the vessels at the periphery of the thyroid gland. There are several papillary groups [5] within the lymphatics, representing metastatic lung adenocarcinoma.

Metastatic Urothelial Carcinoma

(Left) This metastatic urothelial carcinoma has an opacified cytoplasm, with a well-developed paved appearance [box]. This tumor has metastasized to a thyroid papillary carcinoma. There is intimate blending between the tumors. **(Right)** There is blending between the metastatic breast carcinoma cells [box] and the background thyroid gland parenchyma. In cases like this, the separation between a primary vs. metastatic tumor can be quite challenging, though frequently made easier by immunohistochemistry.

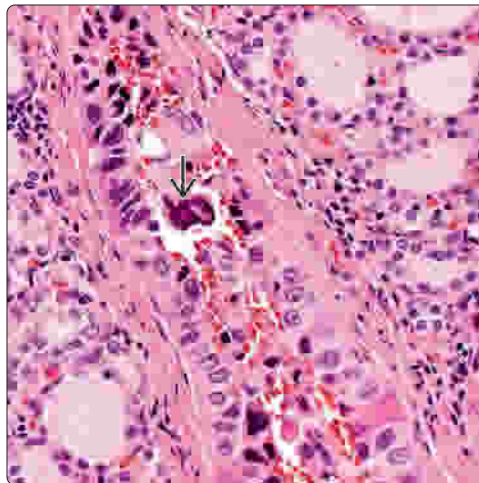


Metastatic Breast Carcinoma

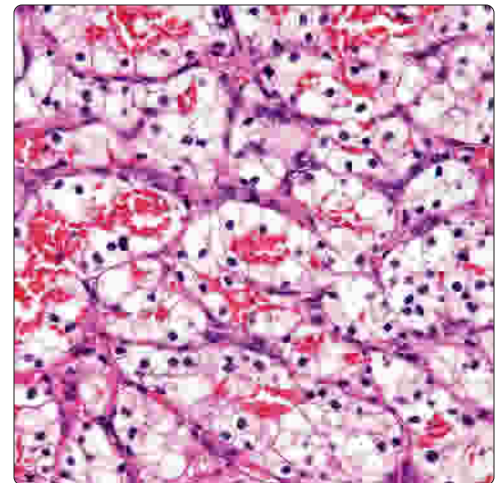


Septum Widened by Metastatic Tumor

(Left) The interlobar septum is widened, with metastatic lung adenocarcinoma filling the lymphatic channel. Note the calcification [box], as well as tall cell appearance, of these neoplastic cells, a mimic of thyroid papillary carcinoma. **(Right)** A rich vascular network divides this metastatic clear cell RCC into a pseudoalveolar pattern with extravasated erythrocytes filling the spaces. There are very distinct cell membranes and small nuclei.

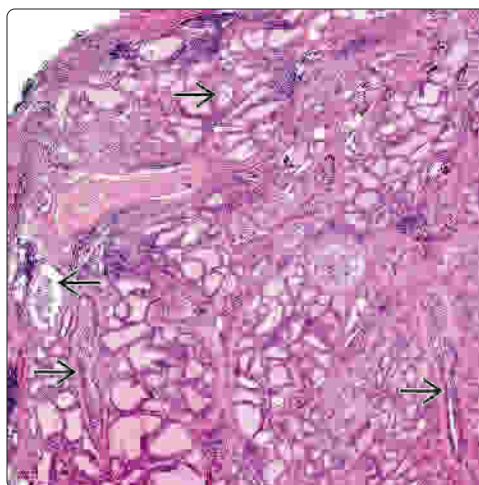


Metastatic Renal Cell Carcinoma

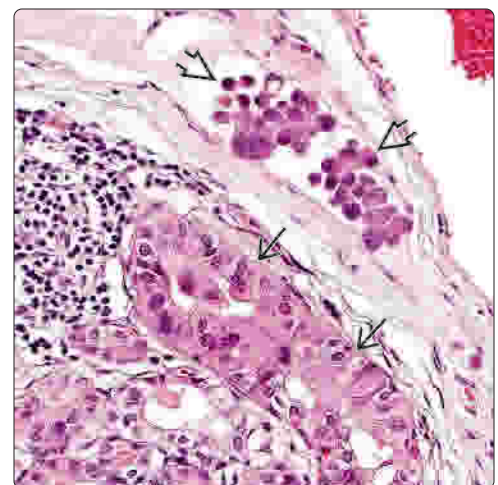


Tumor Emboli Within Thyroid Parenchyma

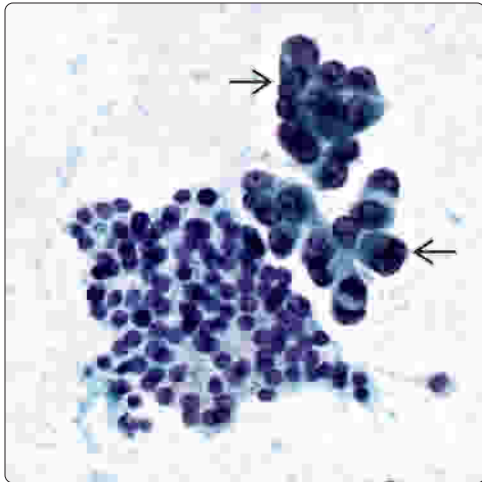
(Left) The thyroid shows a background of adenomatoid nodules and focal chronic lymphocytic thyroiditis. There are numerous lymphatics filled with tumor emboli [box] from a lung adenocarcinoma. **(Right)** There is a morphologic difference between the thyroid papillary carcinoma [box] and the metastatic lung adenocarcinoma [box] noted within the lymphatics. Sometimes intravascular tumors assume a papillary configuration, as seen here.



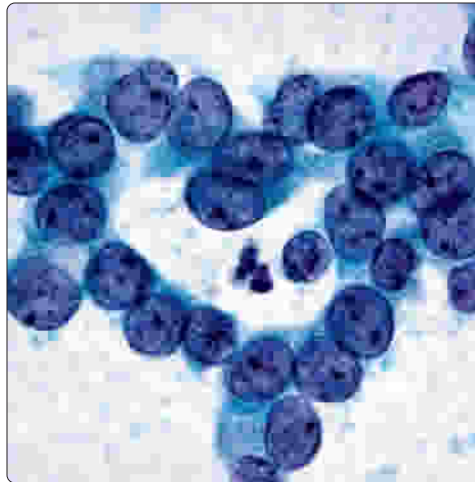
Metastatic Lung Adenocarcinoma



2 Distinct Cell Populations

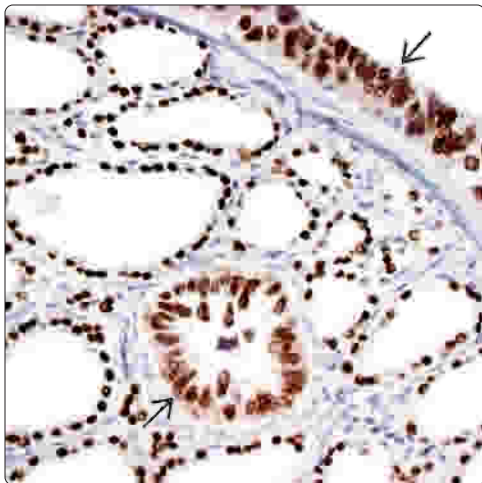


Metastatic Adenocarcinoma

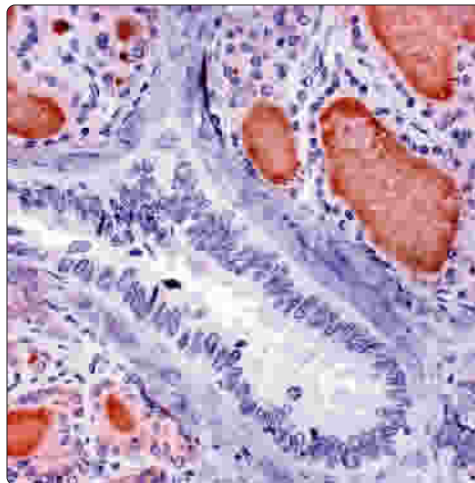


(Left) There is a background of normal thyroid parenchyma, distinctly different from the cohesive clusters of epithelial cells [2]. There is a suggestion of mucin production in this adenocarcinoma. (Right) A high-power view shows gland formation. The chromatin is quite delicate with small nucleoli. It is easy to see how this could be a mimic of thyroid papillary carcinoma.

TTF-1 Showing Variable Reactivity

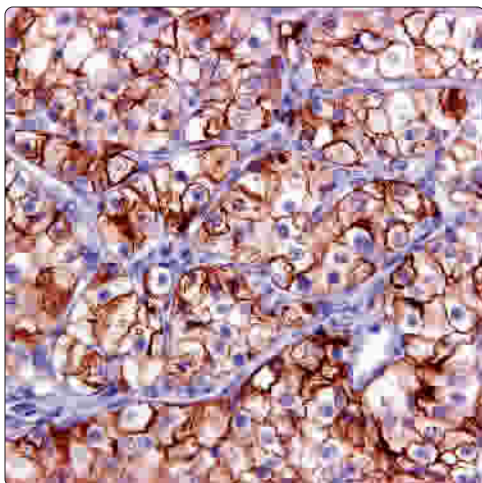


Negative Thyroglobulin in Metastatic Tumor

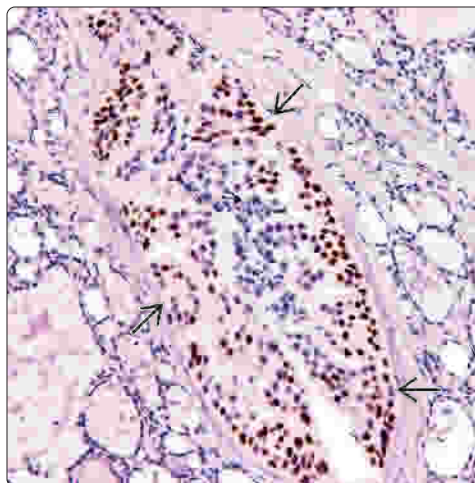


(Left) An example of the different staining appearance with TTF-1 as it highlights the metastatic lung adenocarcinoma [2] with a different intensity than the uninvolved thyroid parenchyma. However, this marker must be interpreted with caution. (Right) Thyroglobulin highlights the native thyroid follicles but does not stain the metastatic lung adenocarcinoma within the lymphatic channel. Negative staining for thyroglobulin can be quite helpful in separating primary from metastatic tumors.

RCC Strongly Highlights Renal Cell Carcinoma



Estrogen Receptor Reaction in Breast Carcinoma



(Left) Metastatic renal cell carcinoma is strongly and diffusely immunoreactive with RCC, highlighting the membranous reactivity. This stain is not unique to RCC but is usually nonreactive in primary thyroid gland lesions. (Right) Estrogen receptor highlights a tumor embolism within a lymphatic space [2]. Note the negative thyroid parenchyma surrounding the lymphatic space. Differential immunoreactivity for selected antibodies is very useful in this setting.

PRIMARY TUMOR

Specimen

- Lobectomy, partial or total thyroidectomy, \pm central or lateral neck dissection
- Tumor focality: Unifocal, multifocal (ipsilateral, bilateral, midline); use "m" for multifocal
- Tumor size (largest tumor) in centimeters
- Capsule: Presence or absence, partial or complete

Histologic Type

- Papillary (variant type, if present), follicular, poorly differentiated, undifferentiated & medullary carcinoma(s)
- Tumor architecture: Follicular, papillary, diffuse, macrofollicular, solid, cribriform-morular
- Cytomorphology: Classical, columnar, and tall cell (for papillary), with clear cell and oncocytic for other tumors
- Well differentiated; tumor necrosis & $> 4/10$ HPF mitoses use poorly differentiated; undifferentiated is grade 4 by definition
- Report additional pathology findings

Invasion

- Tumor capsular invasion
 - Present and extent (minimal, widely invasive)
 - Extrathyroidal extension (soft tissue, skeletal muscle) present and extent (minimal or extensive)
- Lymphatic invasion
 - Present and extent (< 4 or ≥ 4 vessels)
- Vascular invasion
 - Present, type (vein or artery) and extent (< 4 or ≥ 4 vessels)
- Perineural invasion
 - Present or not identified
- Tumor margins: Involved by tumor, comment on location (as oriented)

Tumor Category

- Solitary (s) or multifocal (m): Largest tumor is staged
- T1: Tumor ≤ 2 cm, limited to thyroid gland
 - T1a: Tumor ≤ 1 cm, limited to thyroid gland

- T1b: Tumor > 1 but ≤ 2 cm, limited to thyroid gland
- T2: Tumor ≥ 2 but ≤ 4 cm, limited to thyroid gland
- T3: Tumor > 4 cm limited to thyroid gland, or any tumor with minimal extrathyroidal extension
- T4: Advanced disease
 - T4a: Any size tumor invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
 - T4b: Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels

REGIONAL LYMPH NODES

Cervical Lymph Nodes: Site and Number

- N1a: Metastasis to level VI lymph nodes (pretracheal, paratracheal, prelaryngeal/Delphian, perithyroidal)
- N1b: Metastasis to unilateral, bilateral, or contralateral cervical (levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (level VII)
- Extracapsular extension outside the lymph node reported, if present

PROGNOSTIC GROUPS

< 45 Years (Papillary and Follicular Carcinoma)

- Group I: Any T and any N with no distant metastasis
- Group II: Any T and any N with distant metastasis

≥ 45 Years (Papillary and Follicular Carcinoma)

- Group I and II: T1 and T2, respectively, without lymph node metastases
- Group III: T1, T2, and T3 with N1a or T3 N0
- Group IV: Separated into A, B, C
 - IVA: T1, T2, T3, and T4a with N1b or T4a with N0 or N1a
 - IVB: T4b and any N
 - IVC: Any T, any N, and M1

Medullary Carcinoma (All Ages)

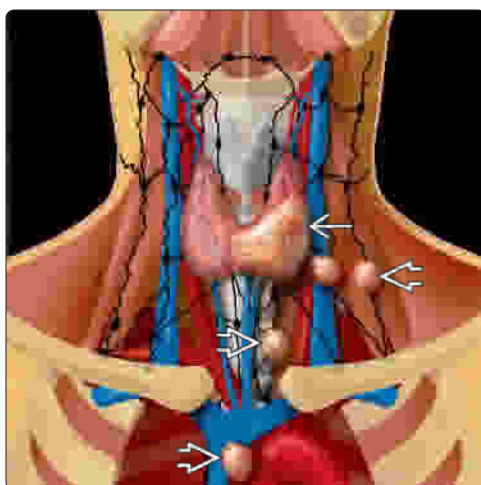
- Groups I, II, III, IVA, IVB, and IVC based on primary site, lymph node metastasis and distant metastasis

Undifferentiated Carcinoma (All Ages)

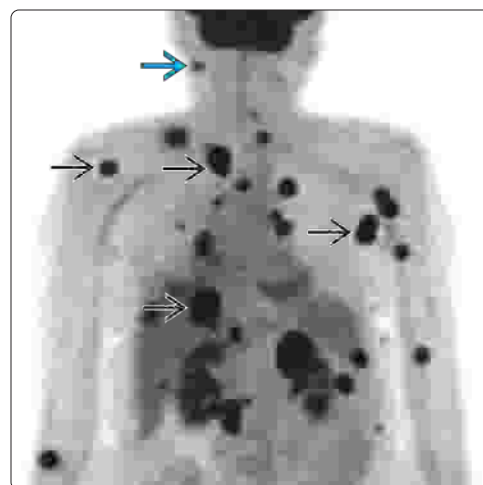
- All tumors are stage IV by definition

(Left) Coronal graphic shows a left lobe thyroid carcinoma with multiple foci of metastatic tumor to cervical and superior mediastinal lymph nodes. (Right) In order of frequency, metastases develop in cervical lymph nodes, lung, bone, liver, and central nervous system, with many different sites concurrently shown in this coronal PET MIP of a patient with known papillary thyroid carcinoma.

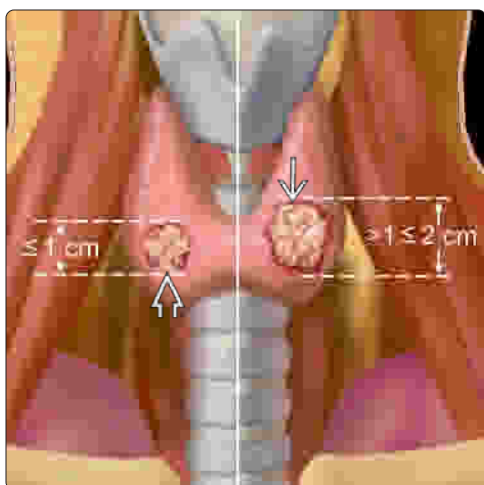
Coronal Graphic of Metastatic Carcinoma



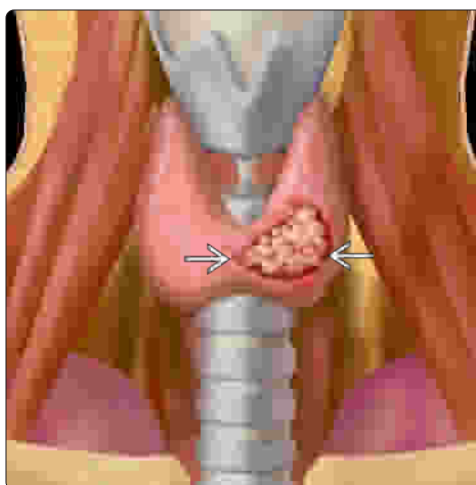
Multifocal Thyroid Carcinoma Metastases



T1 Primary Thyroid Carcinoma

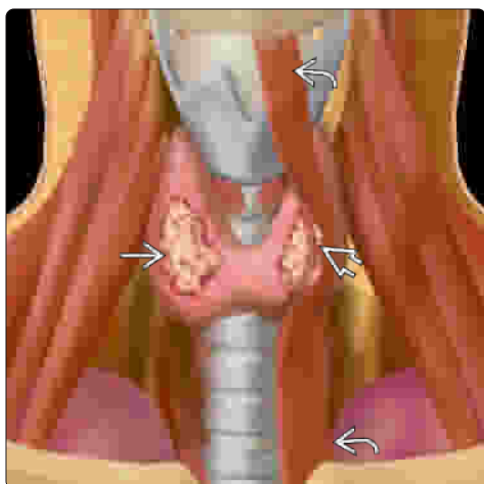


T2 Primary Thyroid Carcinoma

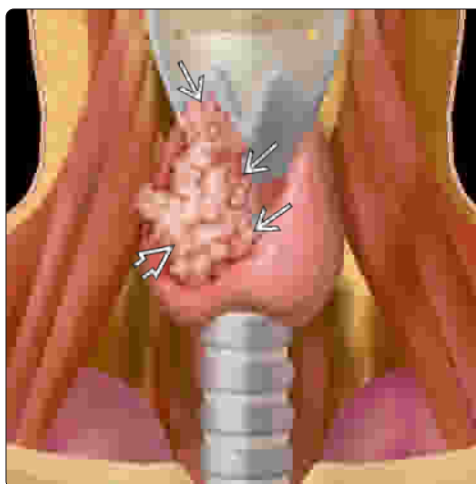


(Left) Coronal graphic illustrates the distinction between a T1a (≤ 1 cm) tumor and a T1b tumor, which is 1-2 cm in size. All T1 carcinomas are contained within the thyroid gland. If multifocal, the T staging is determined by the largest tumor. (Right) Coronal graphic demonstrates a T2 primary thyroid carcinoma, confined to the thyroid gland, > 2 cm but ≤ 4 cm in size.

T3 Thyroid Primary Carcinoma

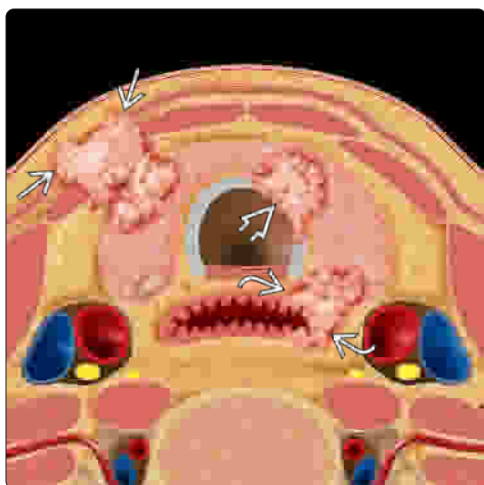


T4 Thyroid Primary Carcinoma

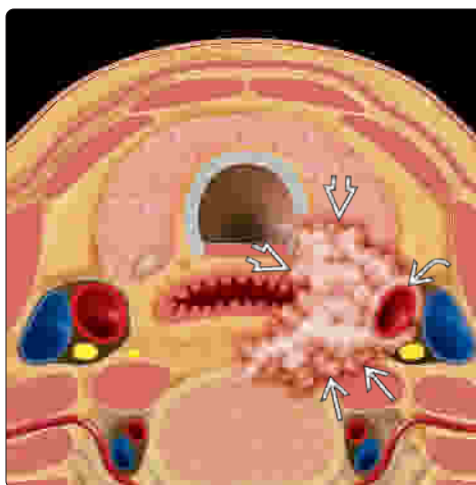


(Left) Coronal graphic shows 2 carcinomas within the thyroid gland, both T3 tumors based on size > 4 cm. The tumor in the right lobe is thyroid contained, while the left lobe tumor shows extrathyroidal extension to the sternohyoid muscle. (Right) Coronal graphic illustrates a T4a primary thyroid carcinoma. There is invasion of adjacent structures, particularly the larynx. All undifferentiated thyroid carcinomas are pT4 tumors by definition.

Axial Graphic of T4a Thyroid Carcinomas



T4b Primary Thyroid Carcinoma



(Left) Axial graphic demonstrates 3 different thyroid carcinomas with gross extrathyroidal extension (T4a). One extends to subcutaneous tissues, one invades the trachea, and one invades the esophagus with left recurrent laryngeal nerve involvement. (Right) Axial graphic shows a very advanced primary thyroid carcinoma (T4b), with invasion of prevertebral fascia to involve the prevertebral space and encasement of the carotid artery.

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SECTION 10

Parathyroid Glands



Parathyroid	1098
Nonneoplastic	
Parathyroid Hyperplasia	1100
Chronic Parathyroiditis	1106
Tertiary Hyperparathyroidism	1107
Benign Neoplasm	
Parathyroid Adenoma	1108
Malignant Neoplasm	
Parathyroid Carcinoma	1114
Metastatic/Secondary Tumors	1120

MACROSCOPIC

Macroscopic Anatomy

- Most people (~ 95%) have 4 parathyroid glands (PTGs): Paired superior and inferior glands
 - Number varies from 2-12, including supernumerary and ectopic glands
 - Intrathyroidal (3%) and intrathymic (10%) are common ectopic locations
- Small (4-6 mm long, 3-4 mm wide, 1-2 mm thick), yellow-tan, lentiform glands typically abutting posterior thyroid capsule
 - Each gland weighs ~ 30-40 mg but can weigh up to 80 mg; inferior glands are slightly larger
 - Covered by delicate fibrous capsule with small surface vessels
- Location variable, most superior glands (75%) lie posterior to mid-superior thyroid poles; inferior gland locations more variable, most (50%) lie lateral to lower thyroid poles
- Embryologically, paired superior glands originate from more caudal 4th branchial pouches (endoderm), while paired inferior glands originate from more cephalad 3rd branchial pouches
 - Longer descent & comigration with thymus explain more variable location & incidence of intrathymic inferior PTGs

MICROSCOPIC

Microscopic Anatomy

- Thinly encapsulated with fibrous septa extending into parenchyma dividing gland into vague lobules
- Stroma composed of mature adipocytes and fibroconnective tissue with rich vascular supply
 - Amount of stromal adipose tissue **increases** with age; while variable, most adult parathyroid glands contain 20-40% stromal fat
 - Stromal fat:parenchymal cell ratio roughly correlates to functional status; hyperfunctioning glands have less stromal fat
 - Proportion of adipose tissue variably distributed throughout glands and not uniform or predictable




- Chief cells: Parenchymal cells that synthesize and secrete parathyroid hormone
 - Small polygonal cells (6-8 μ m) with pale amphophilic, finely vacuolated cytoplasm and round central nuclei with coarse chromatin and small nucleoli
 - Arranged in small nests and thin cords and separated by stromal adipose tissue
 - Cells are intimately associated with delicate capillary network
 - Some areas with acinar or follicular differentiation containing eosinophilic secretions can be seen
 - Chief cells are positive for cytokeratin, chromogranin A, and parathyroid hormone; hyperfunctioning glands tend to have reduced chromogranin A and parathyroid hormone staining due to degranulation
 - Contain glycogen & intracellular lipid; fat stains (e.g., oil red O) can be used to roughly assess gland function as hyperfunctioning glands have reduced intracytoplasmic lipid
- Oxyphil (oncocytic cells)
 - Larger chief cells (12-20 μ m) that are fewer in number and have abundant, granular eosinophilic cytoplasm; typically arranged in small nodules
 - Number increases with age, similar to oncocytic change in some other organs (i.e., salivary gland)
 - Ultrastructurally, contain numerous irregular mitochondria similar to other oncocytes
- Clear cells are less common and represent chief cells with abundant cytoplasmic glycogen
- Unencapsulated parathyroid tissue can be seen in soft tissue adjacent to parathyroid glands as well as in skeletal muscle, thyroid gland, and thymus
- Intrathyroidal, intrathymic, and other ectopic foci may be sites of otherwise normal parathyroid glands
- Canals of Kürsteiner may be seen adjacent to some PTGs and likely represent source for many parathyroid cysts



PITFALLS/ARTIFACTS

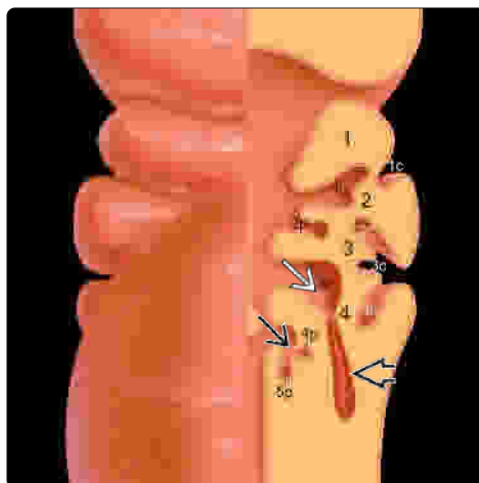
Follicular Change

- Parathyroid with follicular change can mimic thyroid

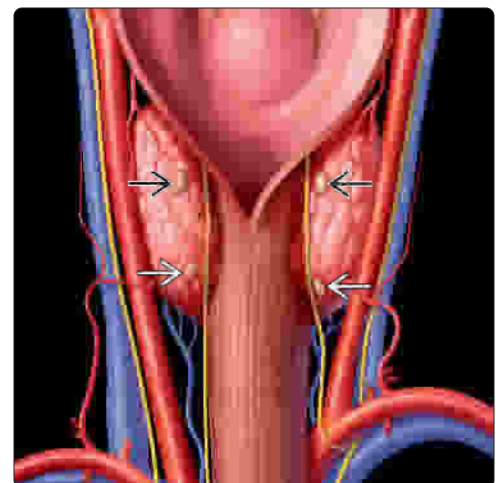
Graphic of Embryologic Development

(Left) Superior parathyroids arise from the 4th branchial pouch  along with the primordial lateral thyroids. Inferior parathyroids arise from the 3rd branchial pouch  along with the thymus .

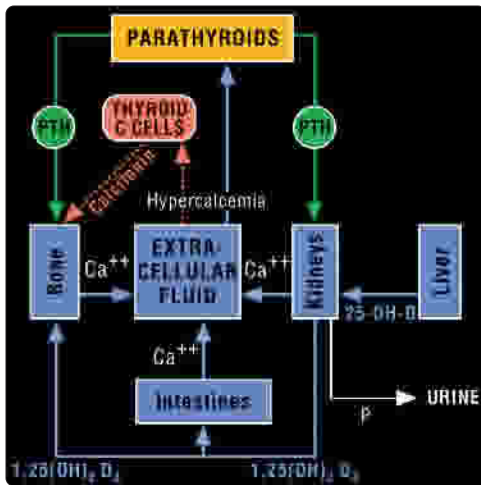
(Right) Most people (~ 95%) have 4 parathyroid glands consisting of paired superior  and inferior glands . Most lie posterior to the thyroid gland poles but can also be found in several variant locations.



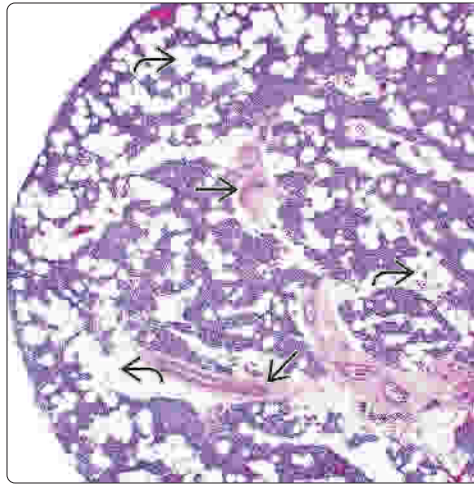
Graphic of Parathyroid Distribution



Parathyroid Hormone Feedback

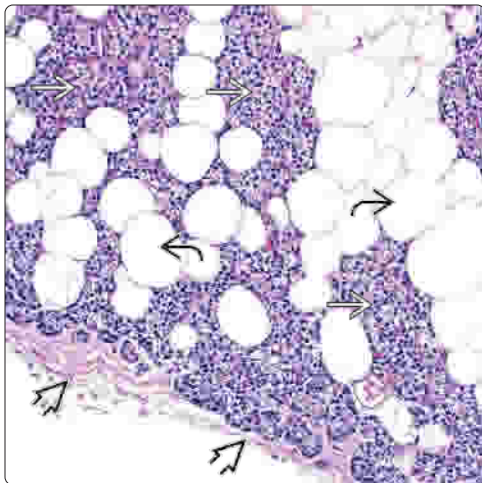


Stromal Adipose Tissue

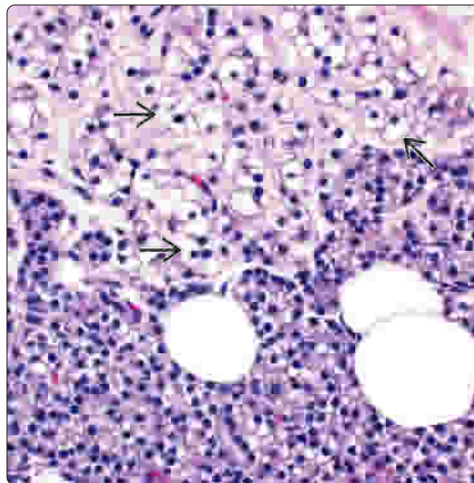


(Left) Calcium metabolism is controlled by a feedback mechanism involving several tissues. Parathyroid hormone (PTH) secretion is stimulated by hypocalcemia and acts to increase serum calcium by resorbing bone and increasing kidney reabsorption and intestinal absorption. PTH also stimulates production of active $1,25(\text{OH})_2$ vitamin D₃. (Right) Although variable, most normal adult parathyroid glands contain around 40% stromal adipose tissue. Large arteries and veins are seen in the septa.

Delicate Fibrous Capsule

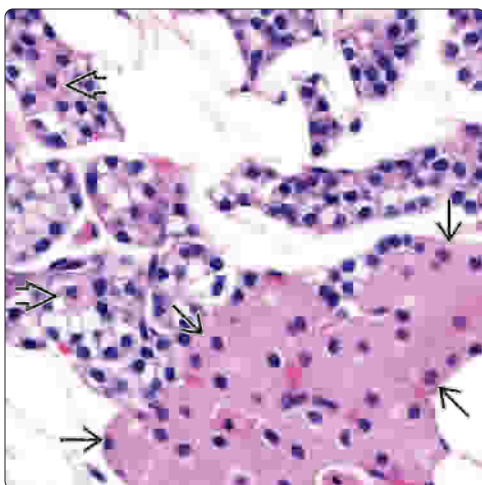


Clear Cells and Chief Cells

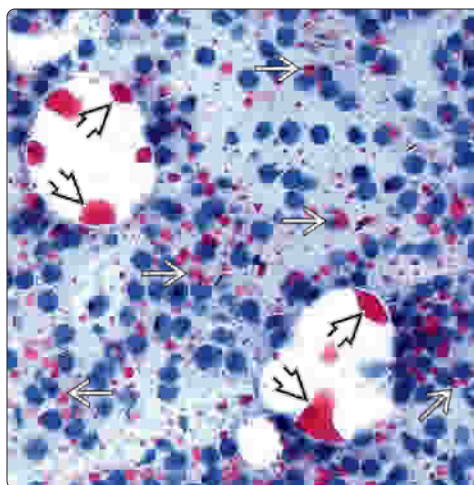


(Left) A delicate fibrous capsule containing small intracapsular vessels surrounds the parathyroid gland. These surface vessels communicate with trabeculae vessels, which receive blood from the hilar (vascular pole) vessels. The chief cells are arranged in nests and cords and are separated by mature stromal adipocytes. (Right) Clear cells are the least common cell type seen in adult parathyroid glands. They also represent altered chief cells, but their cytoplasm is clear due to the accumulation of cytoplasmic glycogen.

Oxyphil (Oncocytic) Cells



Intracellular Lipid



(Left) Oxyphil cells are altered chief cells with abundant, granular, eosinophilic cytoplasm. They have less secretory activity and can be isolated or form small nodules, such as this focus. Transitional forms may be seen. (Right) Chief cells contain intracytoplasmic lipid droplets, highlighted by fat stains on frozen sections, such as this oil red O stain. The amount of cytoplasmic lipid is roughly inversely proportional to secretory activity and is decreased in hyperparathyroid conditions. Mature fat cells also have lipid droplets.

KEY FACTS

TERMINOLOGY

- Nonneoplastic increase in parenchymal cell mass of multiple parathyroid glands in absence of known clinical stimulus for increased secretion of parathyroid hormone (PTH)
- Parathyroid hyperplasia includes
 - Chief cell hyperplasia
 - Water-clear cell hyperplasia

ETIOLOGY/PATHOGENESIS

- Sporadic cases represent 80% of patients with primary chief cell hyperplasia
- ~ 20% of patients with primary chief cell hyperplasia have multiple endocrine neoplasia (MEN)
 - Association most frequent in MEN type 1 (Wermer syndrome)
 - 90% have parathyroid hyperplasia
 - Parathyroid proliferative disease seen in 30-40% of patients with MEN 2A (Sipple syndrome)

CLINICAL ISSUES

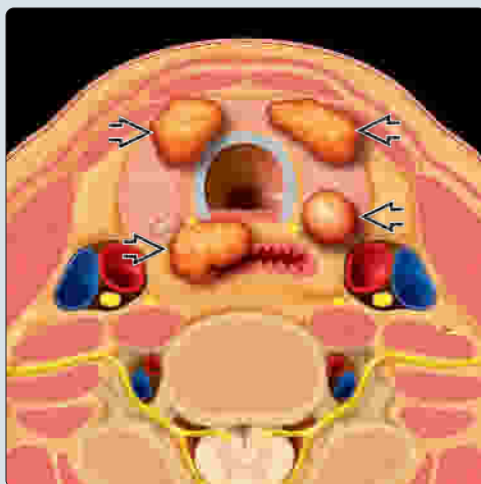
- Chief cell hyperplasia is most common type of hyperplasia causing hyperparathyroidism (HPT)

MICROSCOPIC

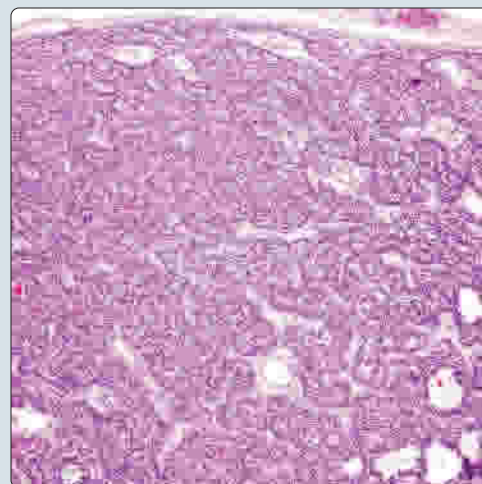
- Increase in parenchymal cell mass (diffuse or nodular)
- **Primary chief cell hyperplasia**
 - Composed of polyhedral cells with round, centrally located nuclei, coarse chromatin, and eosinophilic to amphophilic to clear cytoplasm
 - Oncocytic cells may be present
 - Characterized by striking eosinophilic granular cytoplasm
 - Stromal fat cells absent or markedly decreased in most areas
 - Mitotic figures may be seen
 - Usually < 1 per 10 HPF
- **Water-clear cell hyperplasia**
 - Composed of cells with clear cytoplasm

(Left) Graphic depicts parathyroid hyperplasia with enlargement of all 4 parathyroid glands. More commonly, glandular enlargement is limited to 2, or possibly 3, glands but may only involve 1 gland, making distinction from an adenoma problematic. **(Right)** Diffuse proliferation is shown without intraparenchymal stromal fat and absent rim of the normal/atrophic parathyroid gland. These findings could also be those of an adenoma, requiring biopsy of another gland to determine if more than 1 gland is pathologic.

Multiple Enlarged Parathyroid Glands

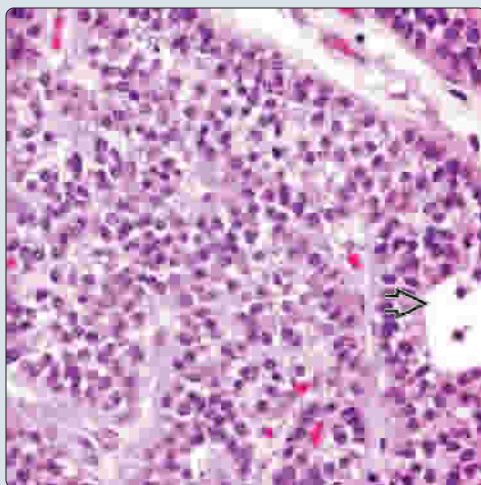


Diffuse Cellular Proliferation With Absent Fat

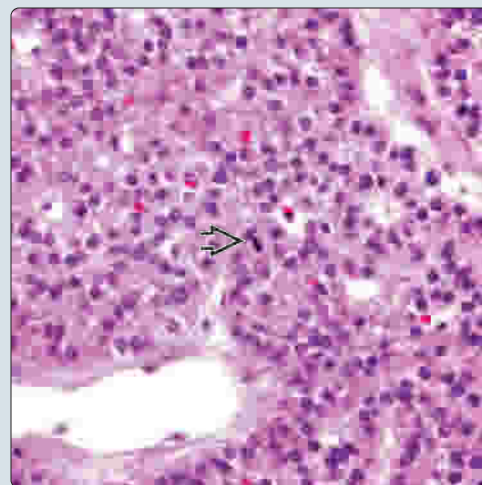


(Left) The cellular proliferation shows a predominance of chief cells arranged in solid sheets and cords focally with a follicular-appearing structure. There is an absence of stromal fat. **(Right)** Parathyroid hyperplasia including a mitotic figure is shown. Increased mitotic figures are not, in and of themselves, diagnostic for parathyroid carcinoma and can be identified in parathyroid hyperplasia and adenoma.

Diffuse Chief Cell Proliferation



Mitotic Activity



TERMINOLOGY

Definitions

- Nonneoplastic increase in parenchymal cell mass of multiple parathyroid glands in absence of known clinical stimulus for increased secretion of parathyroid hormone (PTH)

ETIOLOGY/PATHOGENESIS

Idiopathic

- Sporadic cases represent 80% of patients with primary chief cell hyperplasia

Familial

- 20% have familial disease
 - Usually associated with one of multiple endocrine neoplasia (MEN) syndromes
 - May occur in familial parathyroid hyperplasia without other endocrine abnormalities
- ~ 20% of patients with primary chief cell hyperplasia have MEN
 - Association most frequent in MEN type 1 (Wermer syndrome)
 - Autosomal dominant transmission with variable penetrance
 - 90% have parathyroid hyperplasia
 - Less often associated with parathyroid neoplasms (adenoma and carcinoma)
 - Pancreatic or duodenal endocrine tumors (gastrinoma, insulinoma, glucagonoma)
 - Gastrointestinal endocrine cell hyperplasia or neoplasia (functioning and nonfunctioning)
 - Anterior pituitary adenoma (functioning and nonfunctioning)
 - Some patients also develop pulmonary and thymic neuroendocrine neoplasms, adrenal cortical neoplasms, and thyroid follicular neoplasms
 - *MEN1* gene localized on chromosome 11q13
 - Parathyroid proliferative disease (PPD) seen in 30-40% of patients with MEN 2A (Sipple syndrome) but rare in MEN 2B
 - MEN type 2A (Sipple syndrome) characterized by development of bilateral C-cell hyperplasia, medullary thyroid carcinoma, pheochromocytoma, and parathyroid hyperplasia

Hyperparathyroidism (HPT)

- Represents state of elevated serum PTH as a result of excessive secretion
- Divided into primary, secondary, and tertiary
- **Primary HPT**
 - Inappropriately increased PTH secretion due to intrinsic abnormality of parathyroid gland(s)
 - Occurs in absence of known stimulus for PTH secretion
 - Causes elevation of serum calcium (hypercalcemia) with decreased serum phosphate (hypophosphatemia)
- **Secondary HPT:** Increase in parathyroid parenchymal cell mass of multiple glands in response to known clinical stimulus for increased secretion of PTH

- Usually characterized by hypocalcemia and hyperphosphatemia
- Causes include
 - Chronic renal failure (most common)
 - Dietary vitamin D deficiency or abnormalities of vitamin D metabolism
 - Malabsorption
 - Pseudohypoparathyroidism
- Symptoms primarily related to PTH-mediated bone resorption, which results in
 - Osteomalacia and osteitis fibrosa cystica
- **Tertiary HPT:** Absolute increase in parathyroid parenchymal cell mass associated with autonomous hyperfunction
 - Results in hypercalcemia in patients with known secondary HPT following implementation of dialysis or renal transplantation
 - Hypercalcemia usually develops several years after diagnosis of renal disease
 - Hypercalcemia due to tertiary HPT represents serious threat to renal grafts and requires prompt surgical therapy
 - Laboratory findings similar to those of primary HPT
 - Usually characterized by hypocalcemia and hyperphosphatemia
 - Causes of autonomous hyperfunction of parathyroids in patients with treated renal failure are unknown
 - Elevation of set point for serum calcium postulated
 - Would result in stimulation of parathyroid tissue in spite of normal serum calcium levels
 - Evidence that sheer mass of parathyroid tissue in patients with tertiary HPT may cause autonomous function
 - Removal of bulk of hyperplastic tissue results in readily suppressible remnant
- **Parathyroid proliferative disease (PPD)**
 - Parathyroid gland histopathologic lesions causing HPT collectively referred to as PPD
 - PPD classification includes
 - Parathyroid adenoma causes ~ 85% of HPT cases
 - Parathyroid hyperplasia causes ~ 13-15% of HPT cases
 - Parathyroid carcinoma causes ~ 1-2% of HPT cases

CLINICAL ISSUES

Epidemiology

- Incidence
 - Current reported annual incidence of HPT 0.04 per 1,000 persons
- Age
 - May occur over wide range (2nd-9th decades); mean: 6th decade
 - Incidence increases with age
- Sex
 - Female > male (3:1)

Site

- No specific localization

Presentation

- HPT secondary to parathyroid hyperplasia may be caused by

- Chief cell hyperplasia
- Water-clear cell hyperplasia
- **Chief cell hyperplasia**
 - Most common type of hyperplasia causing HPT
 - Symptoms related to level and duration of serum calcium elevation
 - Patients commonly asymptomatic or present with vague complaints
 - e.g., lethargy, weakness, polyuria, polydipsia, arthralgia, constipation, depression
 - Nonspecific presentation encountered more often in past 2 decades due to
 - Routine biochemical testing resulting overall in increased prevalence in clinically silent cases
 - Signs and symptoms of severe classical primary HPT are uncommon compared to incidence 2-3 decades ago
 - Severe bone disease, once common complication, now rare
 - Bone manifestations more commonly seen may include
 - Diffuse osteopenia ± compression fractures
 - Articular chondrocalcinosis and other joint disorders (e.g., pseudogout, true gout)
 - Renal manifestations also uncommon, may include
 - Nephrolithiasis: Recurrent and severe; stones composed of calcium phosphate
 - Nephrocalcinosis: Presence of bilateral, extensive mineralization in renal pyramids and medullary regions
- **Water-clear cell hyperplasia**
 - Rare cause of HPT
 - Water-clear cell hyperplasia may represent advanced form of chief cell hyperplasia
 - Nephrolithiasis occurs in 90% of patients (vs. 53% in chief cell hyperplasia patients)
 - Overall incidence of bone disease similar to that of chief cell hyperplasia
 - Occasional presentation with osteitis fibrosa generalisata
 - No documented association with MEN or other familial syndromes

Laboratory Tests

- Elevated serum calcium
 - Most accurately reflected by serum ionized calcium value
- Elevated serum PTH levels
 - Normal serum intact PTH levels 210-310 pg/mL
 - Elevations vary depending on type of assay
- Decrease in serum inorganic phosphorus
 - Results from increased urinary loss of phosphates induced by action of PTH at renal tubular level
 - Reflected by decreased tubular reabsorption of phosphate or by increased renal phosphate clearance
 - Corresponding increase in urinary cyclic AMP usually accompanies PTH-induced alterations in urinary phosphate metabolism

Treatment

- Surgical approaches
 - Most widely accepted therapy is subtotal parathyroidectomy with complete removal of 3 glands, leaving remnant of 4th

- Total parathyroidectomy with autotransplantation of remnants of parathyroid tissue in forearm also common surgical therapy
 - Autotransplantation of parathyroid tissue into forearm musculature following total parathyroidectomy may be associated with
 - Graft failure and hypoparathyroidism
 - Recurrent HPT due to hyperplasia of transplanted remnant of parathyroid

Prognosis

- Recurrence rate of HPT following subtotal parathyroidectomy is ~ 16%
 - Recurrences may not be evident for several years
 - Recurrences may be due to inadequate neck exploration, which may result from diagnosis of adenoma in cases of asymmetrical hyperplasia
- Less frequent causes of recurrence include
 - Failure to recognize supernumerary or ectopic glands
 - Parathyromatosis
 - Surgical implantation of hyperplastic tissue in soft tissue of neck
- Recurrence of HPT common problem in patients with chronic renal failure
 - Stimulus for hypersecretion of PTH frequently not correctable

IMAGING

Radiographic Findings

- Imaging procedures less effective in localizing glands in hyperplasia as compared to adenomas or carcinomas
- Tc-99m sestamibi effective in localizing up to 60% of hyperplastic glands
 - Widely utilized in recurrent HPT after parathyroid resection

MACROSCOPIC

General Features

- Distinction between hyperplastic and adenomatous glands generally not made by gross exam
 - Glands with minimal enlargement may be indistinguishable from normal glands
- All 4 glands may be enlarged but
 - Not uncommon for hyperplasia to be asymmetrical with enlargement of only 1, 2, or 3 glands
 - 1 gland may be enlarged, suggesting adenoma
 - Emphasizes need to biopsy grossly "normal" glands to facilitate discrimination between hyperplasia and adenoma
- Diffuse or nodular enlargement
- Soft, tan-brown
- Cystic change may be present but is not common

Size

- Total gland weight in primary chief cell hyperplasia variable
 - < 1 g in ~ 50%
 - 1-5 g in ~ 30%
 - 5-10 g in ~ 20%

MICROSCOPIC

Primary Chief Cell Hyperplasia

- Increase in parenchymal cell mass
 - Predominantly composed of chief cells
 - Polyhedral cells
 - Round, centrally located nuclei with coarse chromatin and well-defined nuclear membrane
 - Cytoplasm is eosinophilic to amphophilic to clear and vacuolated
 - Oncocytic cells may be present
 - Characterized by striking eosinophilic granular cytoplasm
 - Nuclei larger than those in chief cells
- May be diffuse or nodular
 - Arranged in solid sheets, cords, acinar-like or follicular structures, or commonly mixed patterns identified
 - Variable nodularity; nodules may be small (micronodular), solitary or multiple
- Mitotic figures may be seen
 - Usually < 1 per 10 HPF
 - May be increased mitotic rates of 1-5 per HPF
 - Atypical mitoses not present
- Stromal fat cells absent or markedly decreased in most areas
 - Areas with residual fat may simulate appearance of normal gland
 - When identified adjacent to large nodules devoid of fat, may suggest diagnosis of adenoma
- Lipohyperplasia: Term used in cases of hyperplastic glands with abundant fat
 - Presence of fat in this setting makes diagnosis of hyperplasia challenging
 - Biopsies may contain only fat or predominantly fat with limited parenchymal cells
 - Clinical setting and enlargement of multiple glands is of importance in diagnosis of lipohyperplasia

Water-Clear Cell Hyperplasia

- Composed of cells with clear cytoplasm
- May contain multiple cytoplasmic vacuoles

Parathyromatosis

- Nests of hyperplastic parathyroid tissue in soft tissue of neck or mediastinum in primary chief cell hyperplasia
- Probably results from stimulation of embryonic rests of parathyroid cells in primary HPT
- Should not be mistaken for invasion
 - Lack of fibroblastic reaction or infiltrative contour
 - Absence of intravascular location
 - Lack of histologic features of carcinoma
- May be cause of recurrent HPT after apparently complete resection of grossly evident hyperplastic glands

Secondary Hyperparathyroidism

- Proliferation includes chief cells, oxyphilic cells, and transitional cells
- Increased parenchymal cell mass varies depending on duration of disease
 - Parenchymal cells may grow in sheets, cords, or acinar structures

- Nodular aggregates of chief cells or oxyphilic cells common in very enlarged glands
- Oncocytic cells more common component than in primary chief cell hyperplasia
- Presence of residual stromal fat cells varies depending on duration of disease
 - In advanced disease, fat cells are absent
- Areas of fibrosis, cystic change, and calcification may be present

Tertiary Hyperparathyroidism

- 95% of patients have hyperplasia
 - Chief cells predominate in hyperplasia
 - Oncocytic cells may be seen in either diffuse or nodular hyperplasia
 - Rarely, areas with water-clear cells may be present
 - Areas of hemorrhage, fibrosis, and calcification common
 - Mitotic figures, nuclear pleomorphism uncommon
 - Stromal fat cells are sparse but more often present in areas between nodules
 - Distribution may suggest diagnosis of adenoma; however, multinodularity more consistent with hyperplasia
- Only 5% found to have adenomas

ANCILLARY TESTS

Cytology

- Smears indistinguishable from adenoma

Histochemistry

- Periodic acid-Schiff
 - Small follicular structures may contain PAS(+) material
 - Resembles colloid
 - Thyroglobulin negative
- Fat stains (oil red O, Sudan black)
 - Hyperplastic cells
 - Usually contain less intracytoplasmic fat than normal or atrophic parathyroid tissue
 - May contain abundant intracytoplasmic fat
 - Intracytoplasmic fat may be more abundant in chief cells between hyperplastic nodules while usually absent in cells within nodules

Immunohistochemistry

- Chief cells
 - **Positive**
 - PTH, parafibrin, cytokeratins, chromogranin
 - ◻ Staining for PTH and chromogranin is less intense as compared to normal (nonhyperplastic) chief cells
 - **Negative:** thyroglobulin and TTF-1
 - Ki-67 (MIB-1) proliferative index is low
- Clear cells
 - **Positive:** PTH, parafibrin (nuclear), cytokeratins, chromogranin
 - Staining for PTH and chromogranin less intense as compared to normal (nonhyperplastic) chief cells
 - Calcitonin staining may focally be present
 - Cyclin-D1 expression present in majority of cases (~ 61%)
 - Ki-67 (MIB-1) proliferative index is low

DIFFERENTIAL DIAGNOSIS

Parathyroid Adenoma

- Almost always solitary
- Encapsulated to circumscribed
- Absence of stromal fat
- Remnant of normal or atrophic gland may be identified
 - Includes stromal fat

Parathyroid Carcinoma

- Associated with higher levels of serum calcium and PTH
- Single enlarged gland
 - Often adherent to surrounding anatomic structures
- Invasion present in ~ 2/3 of cases, may include
 - Angioinvasion
 - Neurotropism
 - Invasion into adjacent tissues (e.g., thyroid)
- May metastasize

Thyroid Follicular Neoplasm

- Thyroglobulin and TTF-1 (+)
- PTH immunostaining (-)

Metastatic Renal Cell Carcinoma

- May metastasize to cervical lymph nodes
- May share features with water-clear cell hyperplasia
- Immunoreactive for CD10, renal cell carcinoma antigen, carbonic anhydrase IX (CAIX), pax-8
- Immunostaining for PTH is negative

Lithium Therapy

- Associated with form of HPT similar to primary HPT
 - Hypercalcemia, elevated serum parathormone levels
- Both chief cell hyperplasia and adenomas described in these patients
- HPT resolves after discontinuing lithium therapy
- Patients requiring lithium may be treated successfully with subtotal parathyroidectomy

Humoral Hypercalcemia of Malignancy

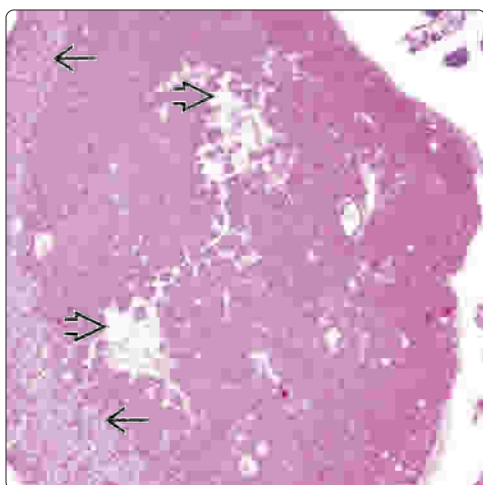
- Important clinical differential diagnostic consideration in patients suspected of primary HPT
- Independent of extent of metastatic disease involving bone
- Characterized by hypercalcemia, hypophosphatemia, elevated urinary cyclic AMP levels
- Unlike HPT
 - Serum parathormone and 1,25-dihydroxyvitamin D suppressed
- Mechanism for hypercalcemia appears to be increased bone resorption
 - Due to humoral factor known as PTH-related protein
- This form of hypercalcemia most frequent in patients with squamous cell carcinoma
 - Lung, upper aerodigestive tract, female genital tract
 - Renal cell carcinoma
 - Urothelial (transitional) cell carcinoma
- 2nd mechanism of hypercalcemia associated with malignancy related directly to osteolytic effect of bone metastases
 - This form of hypercalcemia more common in patients with breast carcinoma and hematologic malignancies
 - Patients have suppressed levels of parathormone but

- Urinary cyclic AMP not elevated
- PTH-related protein not implicated

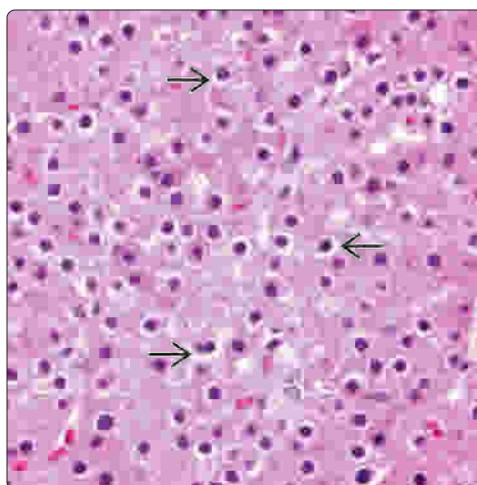
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Oncocytic Cells in Parathyroid Hyperplasia

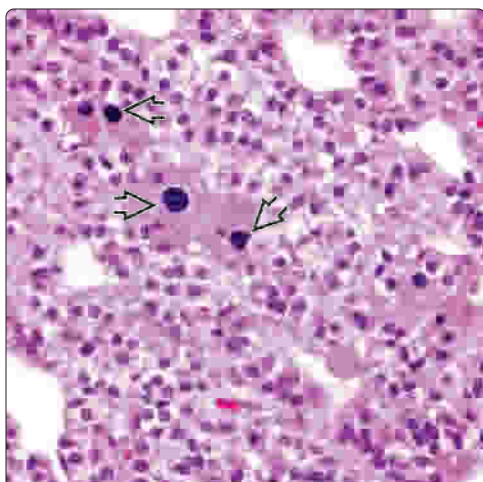


Oncocytic Cells

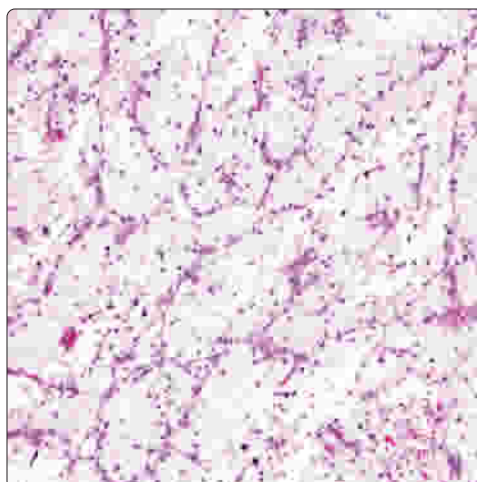


(Left) Hyperplastic gland shows nodular appearance with limited but identifiable stromal fat. It is predominantly composed of oncocytic cells, although chief cells are present. There is an absence of a rim of normal parathyroid tissue. **(Right)** Parathyroid hyperplasia predominantly composed of oncocytic cells, which are characterized by cells with prominent granular and eosinophilic-appearing cytoplasm, is shown. Admixed cells with (in part) clear-appearing cytoplasm are also present.

Endocrine Cell Atypia

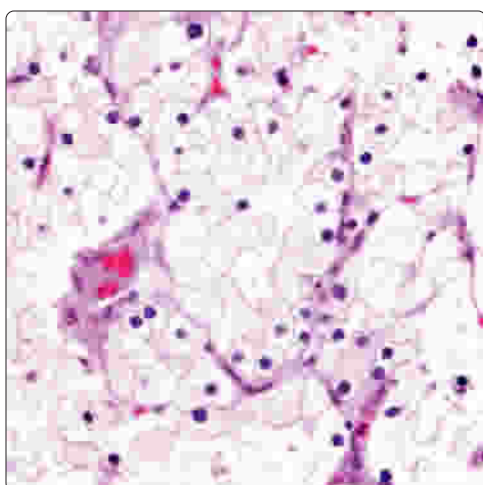


Water-Clear Cell Hyperplasia

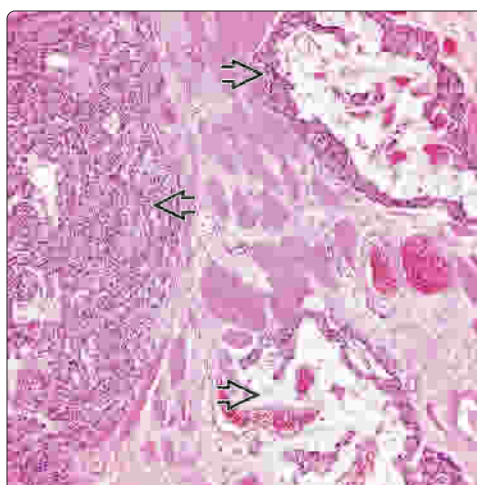


(Left) Diffuse cellular proliferation shows an admixture of chief cells and oncocytic cells; scattered cells with markedly enlarged, pleomorphic, and hyperchromatic nuclei are identified. The presence of endocrine cell (nuclear) atypia is considered to be a reactive finding and not indicative or diagnostic for parathyroid carcinoma. **(Right)** Water-clear cell hyperplasia is a rare cause of hyperparathyroidism showing organoid growth with fibrovascular cores and cells with clear-appearing cytoplasm.

Clear-Appearing Cells



Parathyromatosis



(Left) At higher magnification, the cells in water-clear cell hyperplasia show characteristic clear-to-vacuolated appearing cytoplasm with distinct cell membranes. **(Right)** Parathyromatosis includes nests of hyperplastic parathyroid tissue in the soft tissues of neck, probably resulting from stimulation of embryonic rests. Such foci may be the cause of recurrent hyperparathyroidism after resection of grossly evident hyperplastic glands and should not be mistaken for carcinoma.

KEY FACTS

TERMINOLOGY

- Inflammatory infiltrate within parathyroid parenchyma, possibly related to autoimmunity

ETIOLOGY/PATHOGENESIS

- Poorly understood condition, although thought to be autoimmune
- Lymphocytic infiltration is ongoing destructive process

CLINICAL ISSUES

- Extremely rare
- Older aged patients
- Female > male
- > 1 parathyroid gland may be involved
 - Multifocal disease seen in Sjögren disease (or other autoimmune disorders)
- Most patients are asymptomatic
- Slightly enlarged gland (not usually clinically detected)
- May occur in patients with
 - Hypoparathyroidism
 - Hyperparathyroidism
- Antibodies to parathyroid tissue are seen in only a few cases
- Management is supportive, if clinically necessary
- Significance is unknown

MACROSCOPIC

- Slightly enlarged gland
- Appearance is not specific

MICROSCOPIC

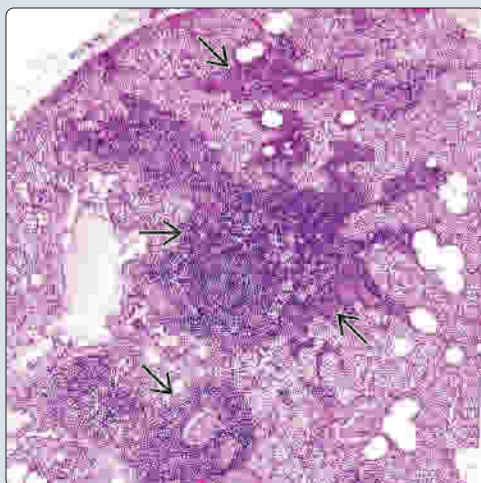
- Aggregates of mature lymphocytes within parathyroid parenchyma
- Parenchyma may be normal or show hyperplasia
- Lymphoid follicle formation may be seen, with germinal centers
- Plasma cells predominate
- Fibrosis separates gland into lobules
- Atrophy may be seen

- Destruction of parenchyma has been reported

TOP DIFFERENTIAL DIAGNOSES

- **Parathyroid infection**
 - Predominantly mature lymphocytes may be seen in viral process
 - Sparse infiltrate with perivascular distribution
- **Parathyroid carcinoma**
 - Significant acellular, eosinophilic fibrosis
 - Invasion of
 - Parenchyma
 - Adipose tissue outside gland
 - Perineural invasion
 - Vascular invasion
 - Presence of necrosis
 - Profound pleomorphism
 - Increased mitoses
- **Lymphoma**
 - May involve parathyroid glands as part of systemic disease
 - Histologic features include
 - Cellular monotony
 - Increased mitoses
 - Tingible body macrophages
 - Immunohistochemical clonality, usually of a B-cell phenotype

Germinal Center Formation



Sheets of Inflammatory Cells



(Left) A low-power micrograph shows sheets of inflammatory cells within the cellular parathyroid gland parenchyma. While there is no well-developed germinal center formation in this case, it is frequently seen in this entity. (Right) There are sheets of lymphoid cells and plasma cells identified immediately adjacent to and intimately involved with the parathyroid parenchyma cells. Note the isolated stromal adipocytes.

KEY FACTS

TERMINOLOGY

- Absolute increase in parathyroid parenchymal mass associated with autonomous hyperfunction
- Hypercalcemia in patient with known secondary hyperparathyroidism following dialysis or renal transplantation

ETIOLOGY/PATHOGENESIS

- Exact cause of autonomous parathyroid gland hyperfunction is unknown
 - Increase in "set point" of calcium is proposed
 - Parathyroid glands are stimulated despite normal serum calcium levels
 - Greatly increased parathyroid parenchymal mass might cause autonomous function
 - If bulk of hyperplastic tissue is removed, remnant seems to be suppressible

CLINICAL ISSUES

- Uncommon
- Wide age range
 - Based on incidence of chronic renal failure
- Equal gender distribution
- Parathyroid gland enlargement
- Hypercalcemia usually develops years after diagnosis of renal disease
 - Hypercalcemia is usually significant threat to renal grafts, requiring prompt surgical therapy
- Laboratory values
 - Elevated ionized calcium
 - Elevated intact parathyroid hormone level
 - May have hypophosphatemia
- Treatment
 - Renal graft may fail if therapy is delayed
 - Subtotal parathyroidectomy is required
- Recurrent hyperparathyroidism can be seen
 - Recurrence of hypercalcemia may be seen in up to 10% of patients

MACROSCOPIC

- Diffuse or nodular enlarged glands
 - May be asymmetric enlargement
- Diffuse hyperplasia: 10-20x normal size
- Nodular hyperplasia: 20-40x normal size

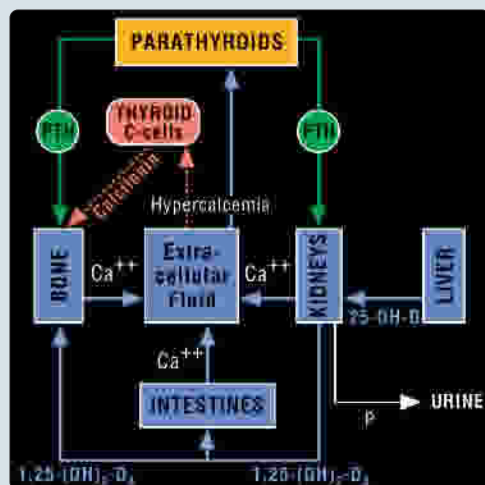
MICROSCOPIC

- Hyperplastic glands are most common presentation (95%)
 - Adenoma accounts for < 5% of tertiary hyperparathyroidism
- Chief cell hyperplasia accounts for majority of parenchyma
 - May have isolated oxyphilic, transitional, or clear cells
- Hemorrhage and fibrosis, sometimes with calcifications, are common
- Nearly absent mitoses and pleomorphism
- Stromal fat is greatly decreased
 - When present, distributed between nodules

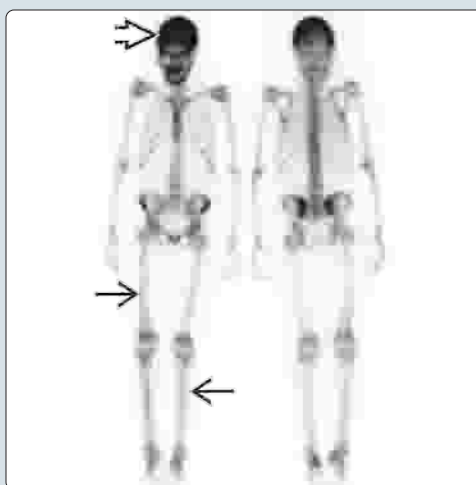
TOP DIFFERENTIAL DIAGNOSES

- **Parathyroid adenoma**
 - Single gland enlargement
 - Atrophic or compressed rim of normal parenchyma at periphery
 - Capsule separating fatless tumor from adjacent parenchyma
 - Usually single tumor cell type, glandular architecture
- **Parathyroid gland hyperplasia**
 - Similar findings to secondary hyperparathyroidism with hyperplasia
 - Requires clinical correlation with serum calcium and parathyroid hormone values
 - Autonomous function must be present

Calcium Metabolism Biofeedback Mechanisms



Bone Scan With Diffusely Increased Uptake



(Left) Calcium metabolism is controlled by a complex biofeedback mechanism that involves several organs. PTH affects kidney and bone to control serum calcium levels. Vitamin D (1,25-[OH]₂-D₃) is also involved in calcium metabolism and includes various conversions in the liver, skin, and intestines. (Right) Anterior and posterior bone scans show diffusely increased uptake in calvaria and axial and appendicular skeleton with absent soft tissue and renal activity, typical of secondary or tertiary hyperparathyroidism.

KEY FACTS

TERMINOLOGY

- Benign neoplasm of parathyroid parenchymal cells, including chief cells &/or oncocytic cells

ETIOLOGY/PATHOGENESIS

- No specific link to any cause
- May be associated with hyperparathyroidism-jaw tumor syndrome (HPT-JT)

CLINICAL ISSUES

- Single most common cause of HPT
- Clinical findings are essentially similar to those of primary HPT due to hyperplasia
 - Serum calcium levels generally higher than in patients with primary chief cell hyperplasia
- 90% of cases affect glands in their usual anatomic location
 - Lower glands are more commonly involved

MICROSCOPIC

- Most are predominantly composed of chief cells

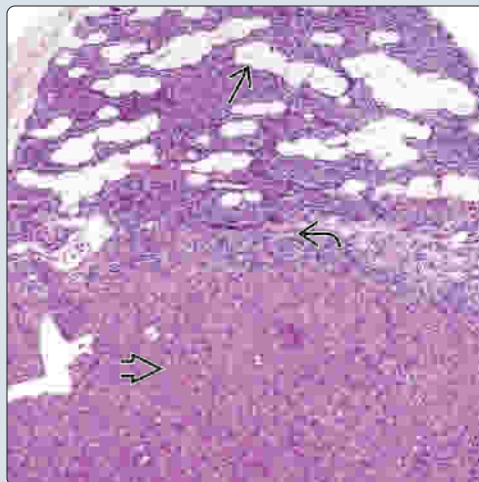
- Oncocytic cells may be present in variable numbers
- Rim of nonneoplastic parathyroid tissue found in association with only ~ 50% of cases
- Oxyphilic adenoma composed of large cells with abundant eosinophilic granular cytoplasm and hyperchromatic nuclei
- Lipoadenoma: Rare benign neoplasm characterized by proliferation of parenchymal and stromal fat cells
- Atypical adenoma: Tumor that shares some features of parathyroid carcinoma but lacks definitive evidence of invasive growth
- Double (multiple) adenomas
 - True double parathyroid adenomas are rare
 - Majority (> 70%) are bilateral; predilecting to superior glands

ANCILLARY TESTS

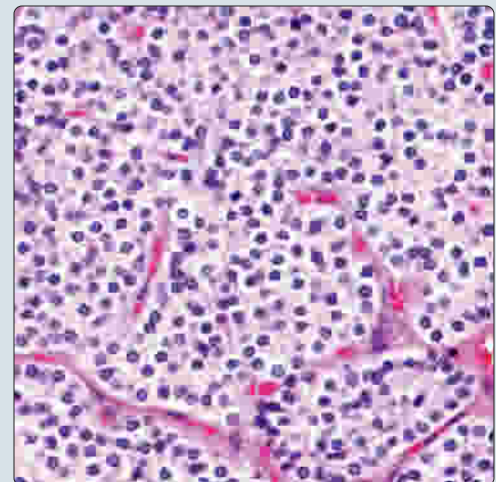
- Positive for parathyroid hormone and parafibromin (nuclear staining)
- Cytokeratin (+), chromogranin (+)

Parathyroid Adenoma

(Left) Parathyroid adenoma shows an increased cellularity and absent intraparenchymal fat. Although unencapsulated, the adenoma is demarcated from the adjacent histologically normal-appearing parathyroid gland characterized by the presence of intraparenchymal fat. (Right) Parathyroid adenoma is exclusively comprised of chief cells that resemble the chief cells of the normal parathyroid gland but typically have larger nuclei than normal chief cells. Note the absence of stromal fat.

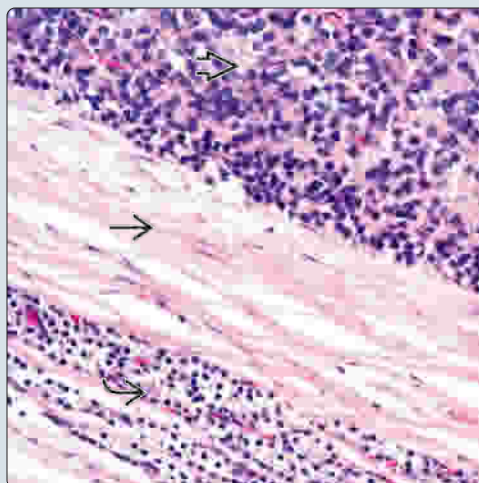


Chief Cells

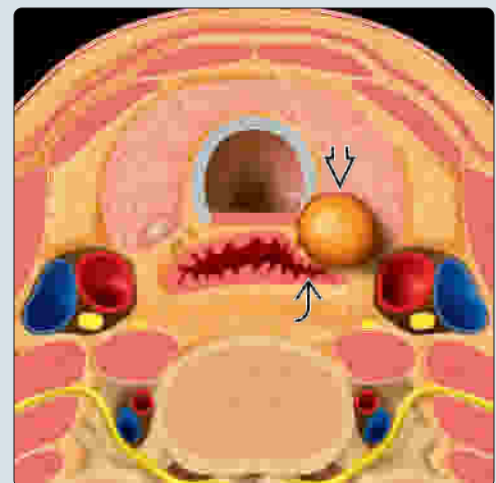


Parathyroid Adenoma and Normal Parathyroid Gland

(Left) The parathyroid adenoma is separated from the residual normal/atrophic-appearing parathyroid gland by the thick capsule. The nuclei of the cells in the parathyroid adenoma are larger than those in the residual normal/atrophic-appearing parathyroid gland. (Right) Graphic depicts a solitary enlarged parathyroid gland characterized by rounded borders with compression of the esophagus but absence of infiltrative growth. Typically, parathyroid adenomas are easily excised.



Parathyroid Adenoma



TERMINOLOGY

Definitions

- Benign neoplasm of parathyroid parenchymal cells, including chief cells &/or oncocyctic cells

ETIOLOGY/PATHOGENESIS

Idiopathic

- No specific link to any cause
- Some evidence supports role of ionizing radiation in development of adenoma

Genetic

- May be associated with hyperparathyroidism-jaw tumor syndrome (HPT-JT)
 - Autosomal dominant disorder with germline mutation in *HRPT-2* gene on chromosome 1q25-31
 - Characterized by
 - Parathyroid adenoma or carcinoma
 - Fibroosseous lesions of jaw (e.g., ossifying fibroma of mandible or maxilla)
 - Renal cysts or tumors
 - Renal lesions may include renal cysts, polycystic renal disease, renal hamartoma
 - Papillary renal cell carcinoma, renal cortical adenomas, Wilms tumor
 - ~ 80% of patients develop HPT
 - Usually presents late in adolescence; hypercalcemia tends to be severe
 - Higher incidence of parathyroid carcinoma in comparison to patients with MEN1 and MEN2A

CLINICAL ISSUES

Epidemiology

- Incidence
 - Single most common cause of HPT
- Age
 - Occurs over broad range
 - Most frequently discovered in 4th-5th decades
- Sex
 - Female > male (3-4:1)

Site

- 90% of cases affect glands in their usual anatomic location
 - Lower glands are more commonly involved
- Less commonly occur in any location where parathyroid tissue may be found
 - Includes ectopic sites such as mediastinum, retroesophageal soft tissue, within thyroid gland, in thymic tissue
- Reports of occurrence in supernumerary glands arising in vagus nerve, pericardium, or other soft tissue sites in neck

Presentation

- Clinical findings are essentially similar to those of primary HPT due to hyperplasia
- Symptomatology changing as result of routine biochemical screening and early detection
 - Hypercalcemia may be incidentally discovered in asymptomatic patients

- Many patients complain only of fatigue, weakness, or depression
- Nephrolithiasis documented in 69% of men and 36% of women but incidence decreasing in recent years to 5-20%
- Severe bone disease, once common complication, now rare
 - Osteopenia (\pm compression fractures) often present
 - Articular chondrocalcinosis and other joint disorders (e.g., pseudogout, true gout)
- Rarely presents as palpable mass

Laboratory Tests

- Serum calcium levels generally higher than in patients with primary chief cell hyperplasia
- Elevated serum parathyroid hormone (PTH) levels
 - Normal serum intact PTH levels 210-310 pg/mL
 - Elevations vary depending on type of assay
- Hypophosphatemia, hyperphosphaturia

Treatment

- Surgical approaches
 - Most widely accepted therapy includes
 - Excision of adenomatous gland
 - Biopsy of at least 1 additional gland normal in size

Prognosis

- Recurrent HPT following surgery may result from
 - Incomplete excision
 - Rupture of tumor capsule with spillage into operative field
 - Hyperfunction of autografted parathyroid tissue following subtotal parathyroidectomy
- Recurrence rates vary significantly and may reflect problems in classification
 - Particularly in cases of hyperplasia with nodules, which may erroneously be diagnosed as adenoma
- Most atypical adenomas prove to be benign tumors in long-term follow-up
 - Treatment similar to typical parathyroid adenoma
 - Patients should be followed for potential
 - Recurrent HPT
 - Local recurrence of tumor
 - Evidence of aggressive behavior (e.g., metastasis)
- Osteitis fibrosa cystica
 - a.k.a. brown tumors
 - May occur in patients with HPT of any etiology
 - Related to degree and duration of serum calcium elevation
 - Lesions characterized by resorption of bone with replacement by fibrous tissue
 - Histology includes
 - Proliferation of multinucleated giant cells and osteoclasts with hemorrhage and hemosiderin deposition
 - Over time degenerative changes occur including cyst formation
 - Cannot be distinguished histologically from giant cell (reparative) granuloma
- Clinical information is essential in diagnosis

IMAGING

General Features

- Several imaging methods used for localization of hyperfunctioning parathyroid tissue, including
 - Retrograde phlebectomy for determination of serum parathormone levels
 - CT scanning, ultrasonography, MR, thallium subtraction scanning, and Tc-99m sestamibi imaging
- Tc-99m sestamibi imaging appears to be most useful
 - Localization of > 90% of adenomas

MACROSCOPIC

General Features

- Almost always solitary
- Significant variation in weight with most 0.3-1.0 g
- Most multiple adenomas probably represent cases of asymmetrical or nodular hyperplasia
- Rounded borders, firm, brown to tan, contained within delicate capsule
 - May be ovoid or lobulated
- Remnant of uninvolved parathyroid tissue at periphery of tumor may be visible
- Cystic change may be present
 - When prominent, may mask neoplastic nature of proliferation
 - Marked cystic degeneration frequently associated with scarring and calcification

MICROSCOPIC

Histologic Features

- Most are predominantly composed of chief cells
 - Cells tend to be larger than nonneoplastic chief cells in uninvolved rim of parathyroid tissue (if present)
 - Nuclei usually slightly larger than those of normal chief cells
 - Nuclei typically round, central to slightly basal location within cell, inconspicuous nucleoli
 - Cytoplasm is typically slightly eosinophilic but may be clear
 - Cells with hyperchromatic enlarged nuclei; multinucleated cells commonly found scattered or clustered in small foci
 - Not indicator of malignancy in absence of other evidence
 - Usually have less intracellular fat than do cells in uninvolved (or suppressed) parathyroid tissue
- Oncocytic cells may be present in variable numbers
 - Either focally admixed with chief cells or as nodular aggregates
 - Some adenomas composed entirely of oncocytic cells
 - Referred to as oxyphilic or oncocytic adenomas
- Cells arranged in sheets, cords, nests, or glandular structures
 - Glandular formations may contain eosinophilic colloid-like material
 - Distinct trabecular pattern uncommon
- Mitotic figures can be found in adenomas
 - Usually number < 1 per 10 HPF

- Mitotic rates as high as 4 mitoses per 10 HPF reported
- Atypical mitoses not present
- Rim of nonneoplastic parathyroid tissue found in association with only ~ 50% of cases
 - If present, this finding is very helpful in making distinction between adenoma and hyperplasia
 - Generally contains abundant stromal fat cells
 - Parenchymal cells smaller than neoplastic cells
 - Generally separated from neoplasm by connective tissue capsule
 - Capsule may be indistinct or absent

Variants

- Oncocytic (oxyphilic) adenoma
 - Composed of large cells with abundant eosinophilic granular cytoplasm and hyperchromatic nuclei
 - Scattered large atypical nuclei or multinucleated cells may be seen
- Lipoadenoma
 - Referred to as parathyroid hamartoma
 - Rare encapsulated neoplasm characterized by proliferation of parenchymal and stromal fat cells
 - May be associated with compressed rim of normal gland
 - May be difficult to recognize as abnormal parathyroid tissue in small biopsy specimens
 - Easily mistaken for normal parathyroid tissue due to abundance of stromal fat
 - Stromal fat often contains areas of fibrosis or myxoid alteration
 - Most associated with HPT
- Atypical adenoma
 - Parathyroid tumor showing features worrisome for parathyroid carcinoma but lacking absolute diagnostic features for parathyroid carcinoma
 - Atypical histologic features may include
 - Capsular irregularities without infiltration of adjacent soft tissues
 - Growth characteristics worrisome for but not diagnostic of invasion (angioinvasion, soft tissue invasion)
 - Increased mitotic activity but < 5 per 10 HPF, absence of atypical mitoses
 - Trabecular growth, intralesional fibrotic bands, spindle-shaped nuclei
- Double (multiple) adenomas
 - Diagnostic criteria for double adenomas include
 - 2 enlarged, hypercellular parathyroid glands
 - Intraoperative confirmation that remaining parathyroid glands are normal &/or biopsy-proven, histologically normal parathyroid glands
 - Absence of family history of MEN or familial HPT
 - Permanent cure of hypercalcemia following excision of enlarged glands
 - Arguably most definitive criterion but requires years of follow-up to include monitoring of serum calcium and parathyroid hormone levels
 - If above criteria are fulfilled, then diagnosis of double adenomas can be confirmed
 - True double parathyroid adenomas are rare
 - Majority (> 70%) are bilateral predilecting to superior glands

ANCILLARY TESTS

Cytology

- Occasionally enlarged parathyroid glands have been subjected to fine-needle aspiration (FNA) as clinically suspected solitary thyroid nodule
- Aspirates of parathyroid tissue typically contain
 - Numerous naked nuclei, as well as small sheets of cells, sometimes forming acinar or follicular structures
 - Small aggregates of dense, colloid-like material may be seen but are not numerous
 - Cells generally small with predominantly round nuclei
 - Nuclei generally hyperchromatic with coarse chromatin typical of neuroendocrine cells
 - Anisonucleosis in scattered cells and occasional large atypical naked nuclei common
 - May-Grünwald-Giemsa or Romanowsky stain
 - Cytoplasm is granular and may exhibit scattered large metachromatic granules
 - Papanicolaou stain
 - Cells have clear to finely granular cytoplasm
 - Distinction from follicular epithelium of thyroid may be difficult
 - Cells are usually smaller than those of thyroid origin
 - Immunohistochemistry helpful in differential diagnosis

Histochemistry

- Fat stains (oil red O, Sudan black)
 - Generally hyperfunctioning cells have significantly decreased amount of intracellular fat compared to normal or suppressed parenchymal cells

Immunohistochemistry

- Positive for parathyroid hormone and parafibromin (nuclear staining)
 - Represents protein product of *HRPT2* gene responsible for HPT-JT syndrome
 - Majority of parathyroid adenomas express parafibromin
 - Loss of parafibromin expression may be seen in patients with HPT-JT syndrome indicative of gene inactivation through mutation of *HRPT2* gene
- Cytokeratin (+), chromogranin (+)
- Calcitonin and synaptophysin typically negative but in small percentage of cases may be focally positive
- PAX8 (nuclear) reactivity present in ~ 40% of adenomas and hyperplasia
- Galectin-3 rarely positive (< 5%)
- Cyclin-D1(+) in <50%
- Negative for thyroglobulin, TTF-1
- Ki-67 (MIB1) proliferative index is low
 - Index > 5% should raise suspicion for carcinoma, but diagnosis of carcinoma requires confirmatory diagnostic findings
 - Proliferative indices in differentiating adenoma from carcinoma are of limited utility given overlapping findings in these lesions

Genetic Testing

- ~ 5% show pericentric inversion of chromosome 11 causing translocation of cyclin-D1 (*CCND1/PRAD1*) gene with parathyroid hormone gene resulting in overexpression of cyclin-D1
- Somatic mutation in *MEN1* gene at 11q13 in 40% of cases
- Absence of *RET* mutation
- 5% have somatic mutation in *CDKN1B* gene (p27Kip1)

DIFFERENTIAL DIAGNOSIS

Parathyroid Hyperplasia

- Multiple glands enlarged and histologically pathologic glands
- Absent rim of normal &/or atrophic parathyroid

Parathyroid Carcinoma

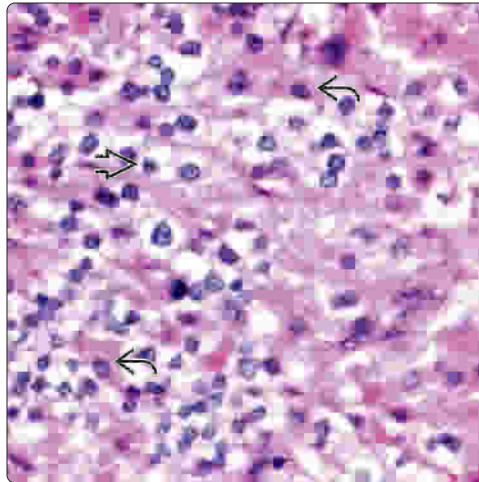
- Typically (but uniformly) associated with higher levels of serum calcium and PTH (than adenoma and hyperplasia)
- Clinically may be adherent to surrounding tissues with difficulties in resection
 - Adenomas (and hyperplasias) usually easily excised and not adherent to surrounding tissues
 - Exceptions occur in presence of prior trauma (e.g., prior surgery, post FNA) resulting in fibrosis
- Diagnostic histologic features include angioinvasion, invasion of adjacent structures (e.g., thyroid, others), neurotropism, metastasis

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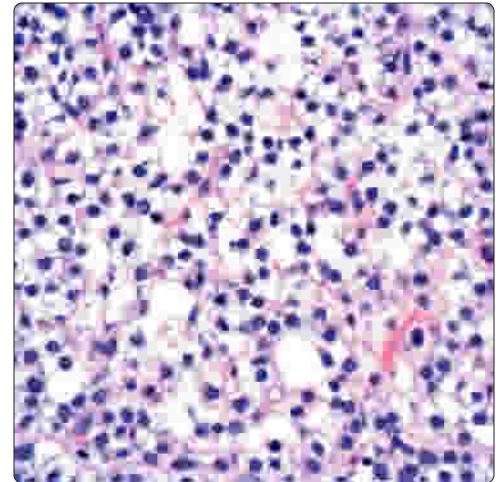
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Admixture of Cell Types

(Left) Admixture of cell types can be seen in parathyroid adenomas, including chief cells with amphophilic to clear cytoplasm and intermixed oncocytic cells characterized by granular, eosinophilic-appearing cytoplasm. **(Right)** While an admixture of cell types can be seen in most parathyroid adenomas, some tumors may be entirely composed of or have areas entirely comprised of single cell types that may include chief cells characterized by clear-appearing cytoplasm.

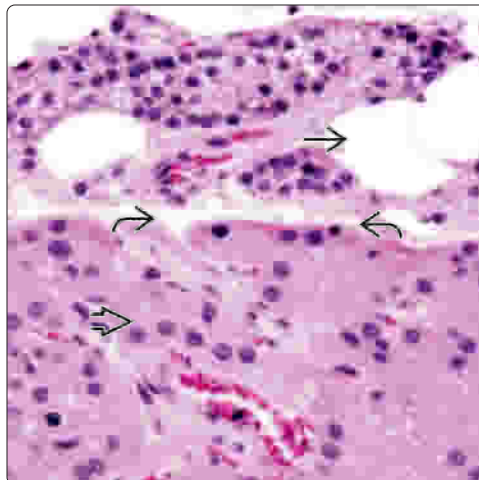


Clear Cells

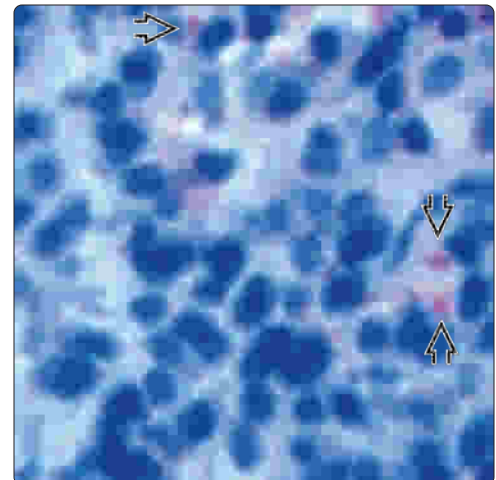


Oncocytic Adenoma

(Left) Parathyroid oncocytic adenoma is entirely composed of oncocytic cells with absent stromal fat. The adenoma is demarcated from a rim of normal parathyroid gland with identifiable stromal fat. Note that the nuclei of the parathyroid adenoma are larger than the nuclei of the nonneoplastic chief cells. **(Right)** Frozen section shows a small amount of fat within the adenoma cells. Decreased lipid is indicative of a hyperfunctioning lesion, as normal cells contain abundant lipid.

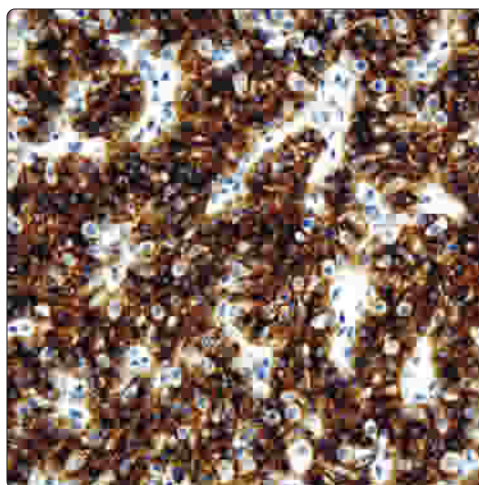


Fat Stain

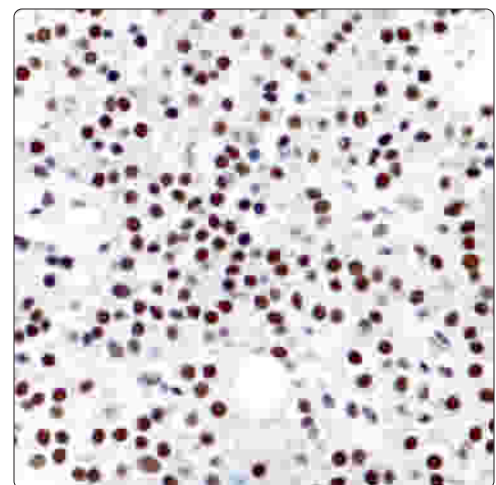


PTH Expression

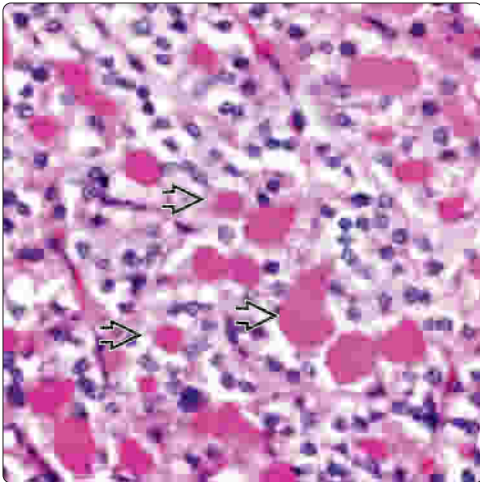
(Left) Parathyroid adenomas express PTH. The expression of PTH is confirmatory of a parathyroid proliferative disease process but does not differentiate between adenoma, hyperplasia, and carcinoma. **(Right)** Parathyroid adenomas typically show diffuse parafibromin (nuclear) staining. While parathyroid carcinomas may have reduced expression of parafibromin, the presence or absence of parafibromin staining does not unequivocally differentiate parathyroid adenoma from parathyroid carcinoma.



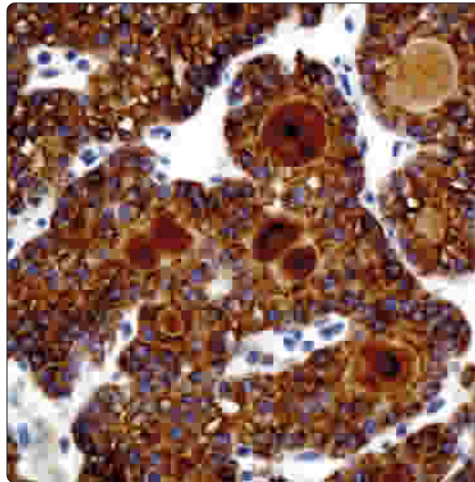
Parafibromin Expression



Follicular Pattern

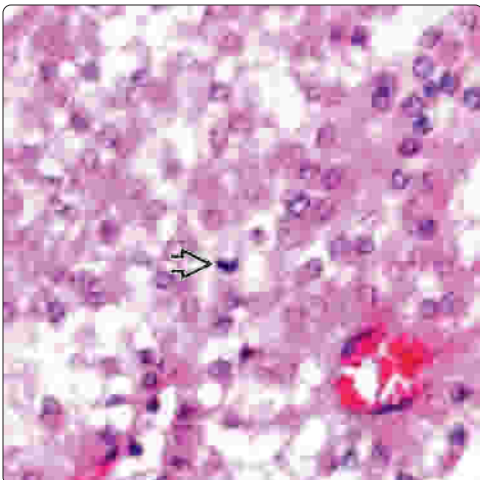


PTH Expression

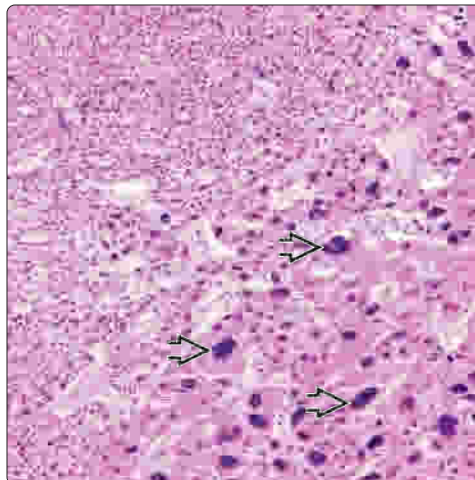


(Left) Parathyroid adenomas may in part or wholly show a follicular growth pattern, including intrafollicular, eosinophilic, colloid-appearing material. Such features may be confused with a thyroid follicular lesion/neoplasm. Similar to colloid, the eosinophilic material in the follicles are PAS(+) but, unlike colloid, is negative for thyroglobulin immunostaining (not shown). **(Right)** The presence of PTH expression confirms this lesion as being of parathyroid rather than thyroid origin in spite of the follicular pattern growth.

Mitotic Figure

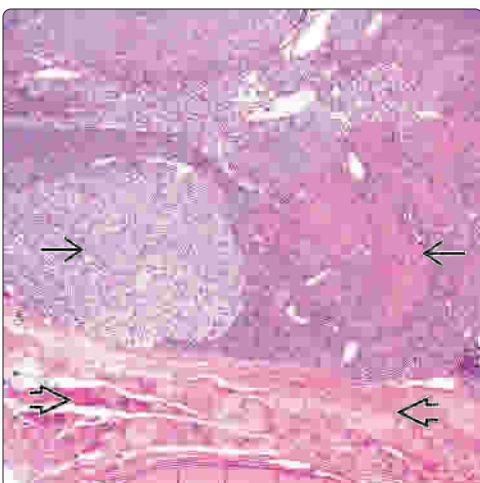


Endocrine Cell Atypia

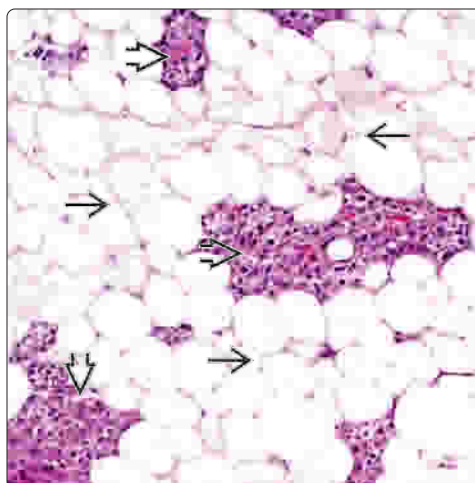


(Left) Parathyroid adenomas may have mitotic figures. Mitoses can be identified in benign parathyroid proliferative disease processes (e.g., hyperplasia, adenoma) and are not, in and of themselves, diagnostic of a parathyroid carcinoma. **(Right)** Endocrine cell atypia characterized by markedly enlarged, pleomorphic, and hyperchromatic nuclei may be seen in a variety of endocrine organ lesions, including parathyroid adenoma, and is not a diagnostic feature of parathyroid carcinoma.

Atypical Parathyroid Adenoma



Lipoadenoma



(Left) Parathyroid adenoma that was difficult to excise, being adherent to the thyroid gland, raising concern for a parathyroid carcinoma is shown. On histologic evaluation, the adenoma approximated but did not invade the thyroid. No other invasive foci were found. Such findings prompted a diagnosis of atypical parathyroid adenoma. **(Right)** Lipoadenomas are distinct parathyroid tumors associated with hyperparathyroidism composed of a proliferation of chief cells with abundant stromal fat cells.

Parathyroid Carcinoma

KEY FACTS

TERMINOLOGY

- Malignant neoplasm of parathyroid parenchymal cells

CLINICAL ISSUES

- Accounts for ~ 1% of primary hyperparathyroidism
- Wide age range (23-75 years), but predominantly older adults (median: 57 years)
- Effects of excessive PTH secretion and hypercalcemia create signs and symptoms
- Simultaneous bone and kidney stone disease more frequent in carcinoma
- Palpable neck mass, often difficult to excise
- Serum calcium > 16 mg/dL, PTH levels > 1,000 ng/L suggests carcinoma
- Overall, indolent tumor with 81% 5-year survival
- Recurrences develop in up to 60% of patients
- Disruption of capsule during surgery can result in parathyromatosis

MICROSCOPIC

- Large tumors with capsular and vascular invasion
- Perineural invasion is nearly pathognomonic
- Prominent, eosinophilic, irregular macronucleoli
- Tumor cell necrosis (comedonecrosis)
- Trabecular growth separated by thick, acellular, band-forming fibrosis


ANCILLARY TESTS

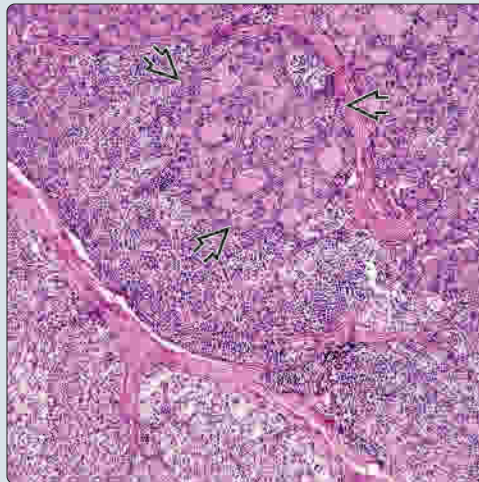
- **Negative:** Parafibromin; **positive:** Protein gene product 9.5 (PGP9.5) is marker of *CDC73* mutation
- Mutations of *HRPT2* (also called *CDC73*), located on 1q25, cause HPT-JT and sporadic parathyroid carcinomas

TOP DIFFERENTIAL DIAGNOSES

- Parathyroid adenoma
- Medullary thyroid carcinoma
- Thyroid follicular neoplasms
- Metastatic renal cell carcinoma

Parathyroid Carcinoma With Thyroid Tissue


(Left) Hematoxylin & eosin shows an invasive parathyroid carcinoma nearly completely surrounding thyroid gland tissue . Adherence to the thyroid gland is one of the histologic features of malignancy. (Right) There is penetration of the capsule by the neoplastic cells, seen associated with periglandular nerves in this parathyroid gland carcinoma. The tumor is cellular, arranged in a trabecular architecture.

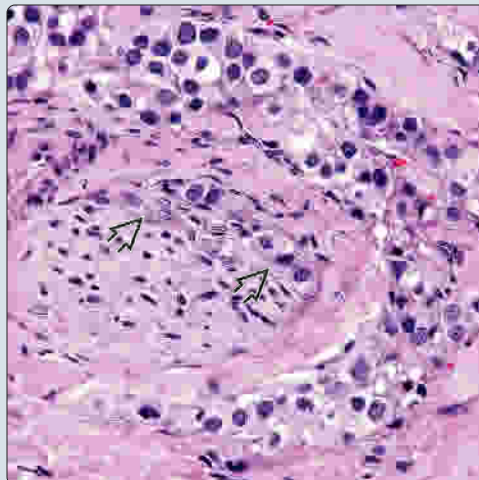


Capsular Invasion

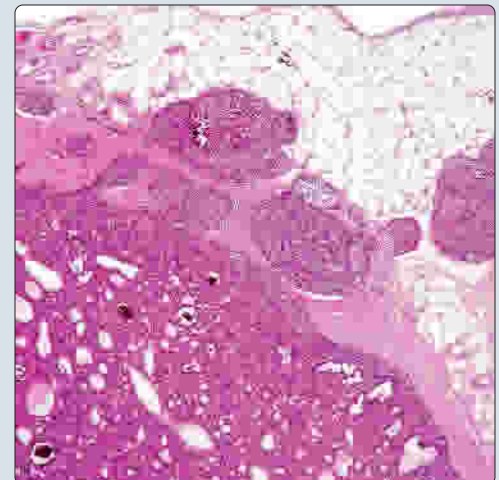


Perineural Invasion

(Left) No one histologic feature is diagnostic for parathyroid carcinoma; intraneural  or perineural invasion is a feature only seen in carcinoma, although only present in about 5% of tumors. (Right) Islands of tumor have invaded beyond the capsule of the neoplasm. This is a finding most suggestive of parathyroid carcinoma.



Parenchymal Invasion



TERMINOLOGY

Abbreviations

- Parathyroid hormone (PTH)
- Hereditary hyperparathyroidism-jaw tumor syndrome (HPT-JT)

Definitions

- Malignant neoplasm of parathyroid parenchymal cells
 - No malignant adipose tumors are recognized in parathyroid

ETIOLOGY/PATHOGENESIS

Irradiation

- Neck irradiation has been suggested as etiologic factor

Inherited

- Autosomal dominant hyperparathyroidism-jaw tumor syndrome (*HRPT2* locus on chromosome 1), yields lifetime risk of parathyroid carcinoma of ~ 15%

Hyperplasia

- Secondary parathyroid hyperplasia is possible risk factor

CLINICAL ISSUES

Epidemiology

- Incidence
 - Accounts for ~ 1% of primary hyperparathyroidism
 - Incidence of < 1/1 million population
- Age
 - Wide range (23-75 years), but predominantly older adults (median 57 years)
- Sex
 - Equal gender distribution
 - Distinctly different from marked female predominance among patients with parathyroid adenomas
 - Further support for de novo development of carcinoma instead of from adenoma
- Ethnicity
 - Japanese patients tend to have higher incidence of carcinoma (~ 5% of primary hyperparathyroidism)

Site

- Arises in any site in which parathyroid tissue may be found
 - Slightly more common in lower parathyroid glands

Presentation

- Effects of excessive parathyroid hormone secretion (PTH) and extremely high calcium levels dictate signs and symptoms (> 90% of tumors are functional)
- Nonspecific symptoms include weakness, fatigue, anorexia, weight loss, nausea, vomiting, polyuria, polydipsia
- Nephrolithiasis, nephrocalcinosis, renal insufficiency and bone "brown tumors" generally develop in patients with high serum calcium levels, a feature more common in carcinoma
 - Concomitant bone and stone disease is more frequent in parathyroid carcinoma than parathyroid adenoma
- Palpable neck mass, often difficult to excise

- Due to adherence to soft tissues, nerves (recurrent laryngeal nerve) &/or thyroid gland
- Identified in up to 75% of patients with carcinoma
- Hoarseness is common with recurrent laryngeal nerve involvement
 - Recurrent laryngeal nerve palsy in patient with primary hyperparathyroidism should suggest possibility of parathyroid carcinoma

Laboratory Tests

- Excessively high serum calcium levels (> 16 mg/dL) are more common in carcinoma
- Extremely high PTH levels (> 1,000 ng/L)
- Frankly elevated serum alkaline phosphatase activity (> 200 IU/L)

Treatment

- Options, risks, complications
 - Must manage metabolic effects of PTH and hypercalcemia (calcimimetics)
 - Recurrent laryngeal nerve damage/involvement can result in hoarseness (up to 60% of patients)
- Surgical approaches
 - Best outcome when there is complete radical resection at first surgery
- Drugs
 - Chemotherapy agents typically ineffective

Prognosis

- Overall, indolent tumor with 81% 5-year survival
 - 10-year survival of ~ 50%, but permanent remission is rarely achieved
 - Positive lymph nodes, older age, black race, number of recurrences and positive surgical margins predict lower overall survival and greater relative risk of death
- Recurrences develop in up to 60% of patients
 - Documented by localization studies in patient with recurrent hypercalcemia
 - Once recurrence is present, cure is unlikely, although palliative surgery gives prolonged survival
 - Average time between surgery and first recurrence is usually < 3 years
- Disruption of capsule during surgery (intraoperative tumor rupture) may cause seeding of parathyroid tissue (parathyromatosis)
 - Associated with overall decreased survival
 - Incisional biopsy is discouraged
- When metastatic disease develops, lung, bone, cervical and mediastinal lymph nodes, and liver are most frequently affected
 - If metastases are found, these patients eventually die from disease
 - Benign "brown tumors" (caused by profound hyperparathyroidism) can mimic bone metastases
 - Ossifying fibromas, component of HPT-JT syndrome, may also mimic bone metastases

IMAGING

General Features

- Tc-99m sestamibi scintigraphy is positive, documenting location, but does not separate adenoma from carcinoma

- Mass is frequently noted, but US, CT and MR do not have specific features

MACROSCOPIC

General Features

- Large tumors, adherent to soft tissues, thyroid gland and nerves
- Firm, gray-white cut surface, sometimes with necrosis
- Must use caution if there has been previous surgery, as scarring and hemorrhage may simulate invasion"

Size

- Range: 1.5-6.0 cm; mean: 3 cm

MICROSCOPIC

Histologic Features

- No one histologic feature, other than metastatic disease, is considered diagnostic for parathyroid carcinoma
- Constellation of features can usually support diagnosis
- Perineural invasion is nearly pathognomonic
 - Present in only about 5% of cases
- Tumor cell necrosis (comedonecrosis)
- Chief cell neoplasms are more common than oncocyctic neoplasms
- Adherence to thyroid gland
- Soft tissue extension
- Capsular invasion
 - Entrapped epithelium in degenerative fibrosis can mimic invasion
 - Autotransplanted hyperplastic parathyroid tissue may give seemingly invasive growth pattern
- Vascular invasion
 - Endothelial-lined space invasion or tumor thrombus in vessel
 - Identified in tumor capsule or in surrounding soft tissue rather than within tumor
- Thick, acellular, band-forming fibrosis between tumor cells
 - Proclivity for perivascular distribution or origin
 - Can be mixed with hemosiderin and hemorrhage
- Trabecular growth is most suggestive of malignancy
 - Solid, diffuse or organoid is suggestive, but not diagnostic
- Perivascular reserve-palisading of tumor cells
- Tumor cell monotony, although profound pleomorphism can be seen
- High nuclear:cytoplasmic ratio
- Spindling of tumor cells
- Prominent, eosinophilic, irregular macronucleoli
- Increased mitotic figures, including atypical forms
 - > 5/50 HPF is worrisome for carcinoma
- Tumor cell spindling, "watermelon seeds," and pyknosis suggest malignancy

Atypical Adenoma

- Intermediate category between adenoma and carcinoma
- Use for parathyroid neoplasm lacking unequivocal evidence of invasiveness, but showing some other feature(s) suspicious for malignancy
- Uncertain malignant potential, requiring close clinical follow-up

- Long-term follow-up usually shows benign course

ANCILLARY TESTS

Cytology

- Separation of thyroid from parathyroid may be difficult
- Does not separate benign from malignant primary tumors
- May be associated with tumor seeding and thus is discouraged

Frozen Sections

- Of no value in separating benign from malignant disease

Immunohistochemistry

- **Positive:** Chromogranin, parathyroid hormone, keratins
- **Negative:** Parafibromin; **positive:** Protein gene product 9.5 (PGP9.5) is marker of *CDC73* mutation
 - Results for carcinoma that are absent in adenoma
 - Parafibromin IHC may be technically difficult to perform

Flow Cytometry

- Unhelpful: Adenomas can be aneuploid and carcinomas are often diploid

Genetic Testing

- Mutations of *HRPT2* (inactivating germline or somatic mutations of tumor suppressor gene), also called cell division cycle 73 (*CDC73*), located on 1q25, cause HPT-JT and sporadic parathyroid carcinomas
 - Gene encodes parafibromin, which is lost in carcinoma (lack of nuclear staining)
 - Bi-allelic inactivation or mutation of *HRPT2* in sporadic tumors
 - Most prevalent mutated gene in parathyroid carcinoma
- Significantly, many genomic alterations in parathyroid adenomas, including 11q (location of *MEN1* gene), are rarely identified in carcinomas
 - Supports de novo development of parathyroid carcinoma (not from adenoma)
 - Parathyroid carcinoma is not proven neoplasm of *MEN1*
- Cyclin-D1 overexpressed in carcinoma
- Recurrent losses of chromosome 13q in parathyroid carcinomas (CGH and molecular allelotyping)
 - 13q is region known to contain retinoblastoma (*RB1*) and *BRCA2* tumor suppressor genes
- LOH in 1p32.3-36.2
- Decreased *Rb* protein expression
- Recurrent germline and somatic mutations in prune homolog 2 (*PRUNE2*) seen in parathyroid carcinoma

DIFFERENTIAL DIAGNOSIS

Parathyroid Adenoma

- Setting of previous surgery or neck manipulation makes separation difficult
- Adenomas are usually smaller, but when adenomas are larger, they tend to have fibrosis, hemosiderin deposits, and cystic degeneration
- Rim of uninvolved/normal parathyroid parenchyma is rarely seen in parathyroid carcinoma
- Cells of adenoma are greatly enlarged and lack conspicuous nucleoli

Immunohistochemistry

Antibody	Reactivity	Staining Pattern	Comment
Chromogranin-A	Positive	Cytoplasmic	Nearly all tumor cells
PTH	Positive	Cytoplasmic	Nearly all tumor cells
CK-PAN	Positive	Cytoplasmic	
CK7	Positive	Cytoplasmic	
CK18	Positive	Cytoplasmic	
RCC	Positive	Cell membrane & cytoplasm	Delicate staining, usually only focal
pax-8	Positive	Nuclear	All neoplastic cells
CD10	Positive	Cell membrane & cytoplasm	Positive in most tumors
EMA	Positive	Cytoplasmic	Reactive in most tumor cells
p16	Positive	Nuclear	
Cyclin-D1	Positive	Nuclear	Overexpressed in most carcinomas
Ki-67	Positive	Nuclear	> 5% may help separate between benign and malignant
S100	Positive		Highlights nerves (not tumor cells) which allow for detection of perineural invasion
Parafibromin	Negative	Nuclear	Usually positive in adenoma but negative in carcinoma
TTF-1	Negative		
Thyroglobulin	Negative		

- Mitotic activity is usually low (> 5% Ki-67 labeling index is worrisome for carcinoma)
- Adenomas **positive** with
 - Parafibromin (negative in carcinoma)
 - p27, Bcl-2, and MDM2

Medullary Thyroid Carcinoma

- Direct extension or metastasis
- Usually not clear cell pattern, showing plasmacytoid cells
- **Positive:** Calcitonin, CEA-m, chromogranin, synaptophysin

Thyroid Follicular Neoplasms

- **Follicular** pattern can be seen in both tumor types
- Thyroid tumors have eosinophilic cytoplasm
 - Parathyroid tumors tend to have clear(er) cytoplasm and prominent cell borders
- **Positive:** TTF-1, thyroglobulin, pax-2; **negative:** Parathyroid hormone, chromogranin

Metastatic Renal Cell Carcinoma

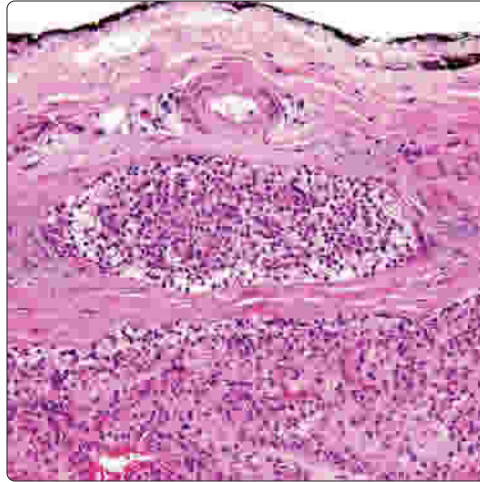
- May present as clear cell neoplasm in parathyroid gland
- Vascular pattern and sinusoidal growth are helpful
- Extravasated erythrocytes may help
- **Positive:** Vimentin, RCC, CD10, EMA, pax-2, CAIX
 - Overlap with parathyroid tumors

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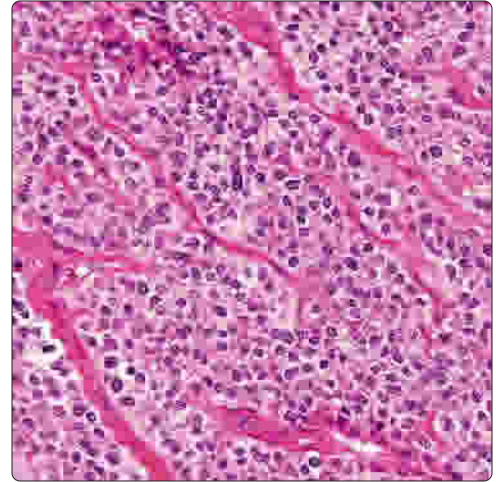
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(Left) Hematoxylin & eosin demonstrates a vessel with the lumen filled with tumor cells. Thrombus of tumor, like this, is not a feature of benign lesions. **(Right)** The neoplastic cells are arranged in a trabecular architecture, separated by delicate fibrous connective tissue bands. Trabeculae are usually 8-10 cells wide. This is usually not a feature seen in adenoma, although focal trabeculae can be seen.

Lymphatic Invasion

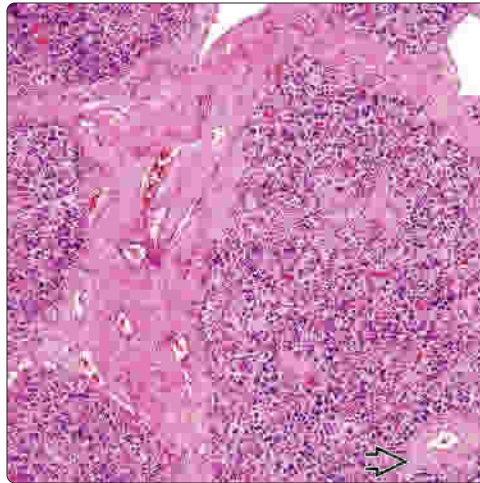


Trabecular Architecture in Carcinoma

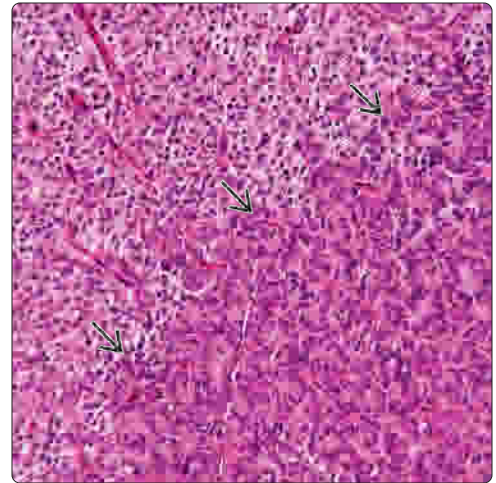


(Left) Heavy, dense, acellular eosinophilic fibrosis is frequently seen in carcinoma. The fibrosis often begins around vessels [B]. There is no associated hemosiderin or degeneration. **(Right)** This tumor shows an abrupt transition from one pattern to another, showing a completely different histologic appearance. The lower portion of the field [B] shows a neoplastic population that has a significantly higher nuclear:cytoplasmic ratio and a more glandular architecture than the top.

Intratumoral Fibrosis Around Vessels

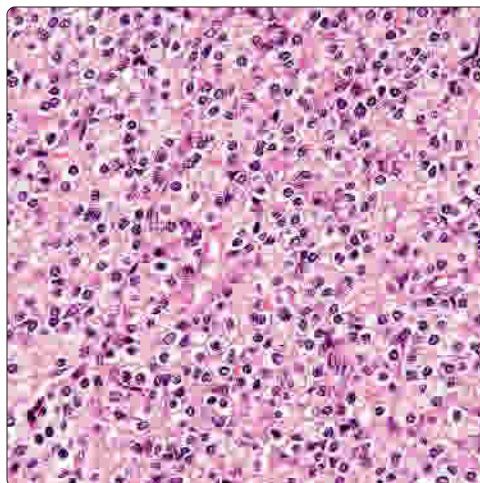


Abrupt Transition to Carcinoma

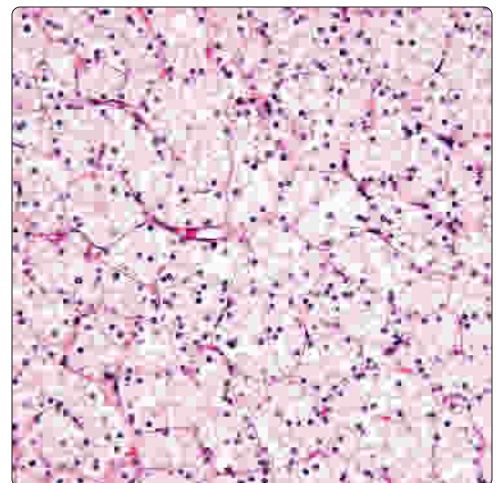


(Left) There is a sheet-like distribution of these neoplastic cells. They possess a high nuclear:cytoplasmic ratio, hyperchromatic nuclei, and a perinuclear halo, highlighting the prominent cellular borders. **(Right)** Clear cell change is not a common finding in parathyroid carcinoma. This tumor, if viewed on high power only, does not show the characteristics of parathyroid carcinoma, even though the tumor had necrosis and perineural invasion elsewhere.

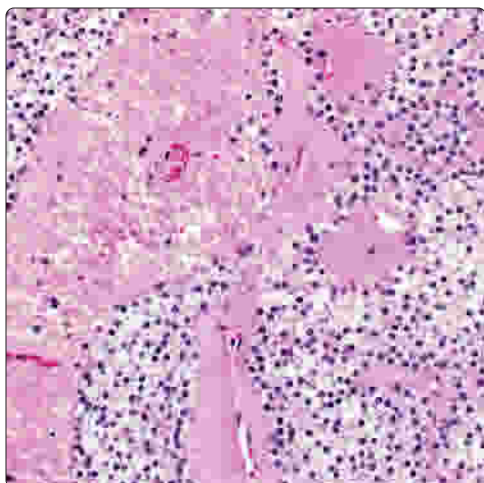
Sheet-Like Growth of Atypical Tumor Cells



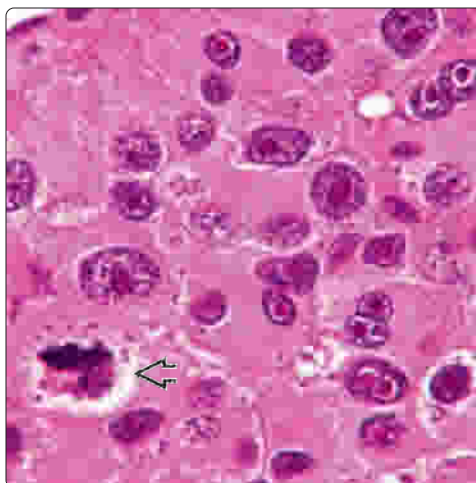
Clear Cell Change in Carcinoma




Comedonecrosis

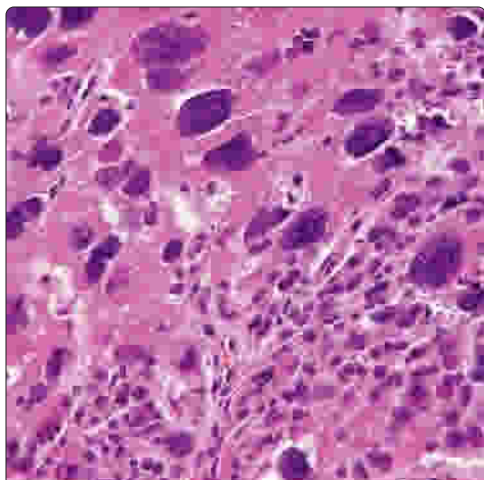


Prominent, Irregular Macronucleoli

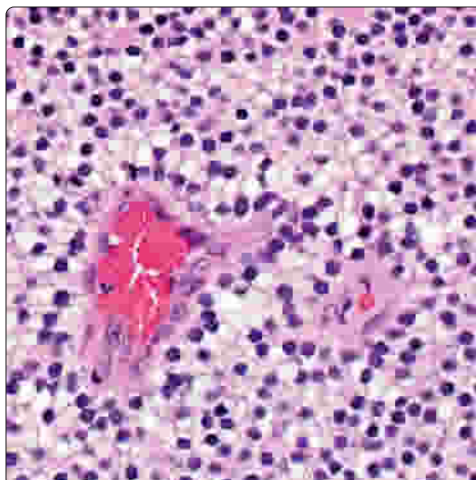


(Left) There is well-developed tumor necrosis (comedonecrosis) in this example of parathyroid carcinoma. The tumor cells show cytoplasmic clearing, but the nuclei are bland in appearance. **(Right)** Very large neoplastic cells with prominent, brightly eosinophilic, and irregular macronucleoli are shown. There is a perinucleolar halo, a finding seen in carcinoma. Note the atypical mitotic figure .

Profound Nuclear Pleomorphism

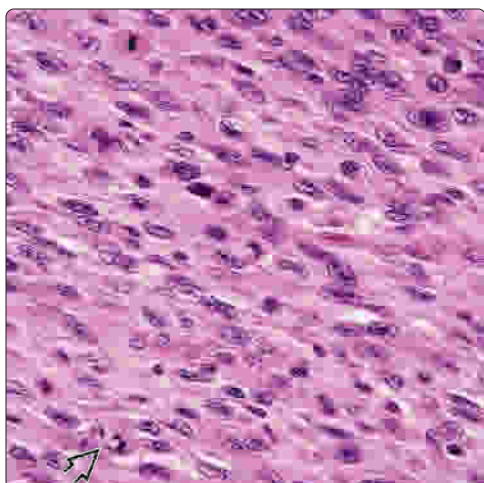


Reverse Polarization

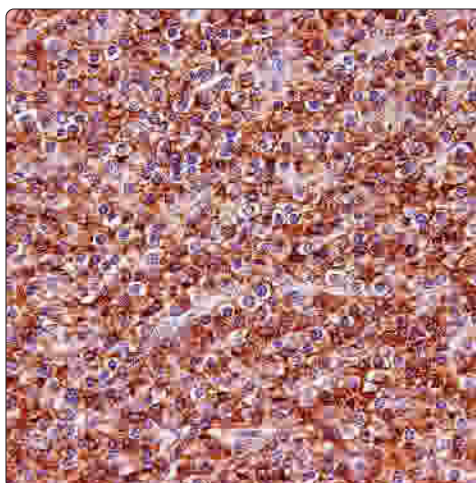



(Left) Profound nuclear pleomorphism is noted in this tumor. There are more than just isolated atypical cells. Here there is a sheet-like distribution of the atypical neoplastic cells. **(Right)** It is not uncommon in parathyroid carcinoma to see areas of reverse polarization: This is when the nuclei are separated from the vessel wall by a cleared, subnuclear vacuole.

Sarcomatoid or Spindled Cell Pattern



Strong and Diffuse Chromogranin Reaction



(Left) Although uncommon, a predominantly or focally spindle cell pattern can be seen in carcinoma. There are mitotic figures, including an atypical form . Typical glandular features of parathyroid tissue are usually identified somewhere within the tumor. **(Right)** Chromogranin is generally positive in parathyroid tissue. In this case, there is a membrane reactivity, although often a granular cytoplasmic reaction is present. Immunohistochemistry alone does not confirm carcinoma.

KEY FACTS

TERMINOLOGY

- Tumors secondarily involving parathyroid gland as result of hematogenous/lymphatic spread from primary malignancies of distant sites

ETIOLOGY/PATHOGENESIS

- Abnormal parathyroid tissue (hyperplasia, adenoma, carcinoma) seem to contain metastases more frequently than normal tissue
- Alterations in vascularity or blood flow may contribute to metastatic disease development

CLINICAL ISSUES

- < 0.1% of parathyroid glands removed surgically
- Carcinomas are most common
 - Breast (lobular > ductal), lung, kidney
- Metastases to parathyroid gland correlate with poor prognosis
- < 0.1% of parathyroid glands removed surgically

- Female > male (1.2:1)
- Vast majority of patients are asymptomatic
- Melanoma, soft tissue sarcomas
- Parathyroidectomy, especially if slow-growing tumor or isolated metastasis

MACROSCOPIC

- Wide range, but vast majority are microscopic

MICROSCOPIC

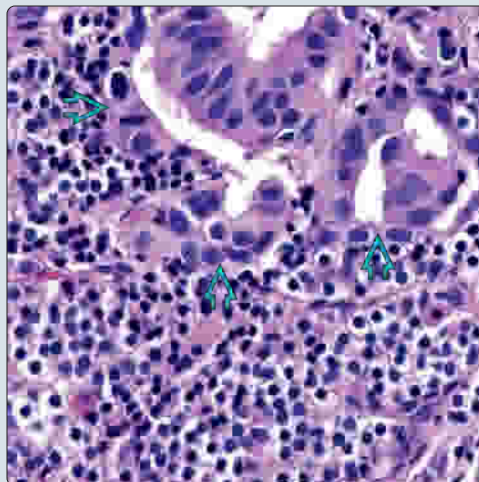
- Features of primary tumor are usually maintained
- Lymphovascular location of tumor emboli

TOP DIFFERENTIAL DIAGNOSES

- Clear cell adenoma
- Medullary carcinoma

(Left) A metastatic breast adenocarcinoma is identified within the parenchyma of a parathyroid adenoma. Metastases are identified in abnormal parathyroid tissue more often than in normal tissue. **(Right)** There is an intimate relationship between the parathyroid parenchyma and the paraganglioma. Separation of these 2 elements would require immunohistochemical evaluation.

Metastatic Breast Carcinoma

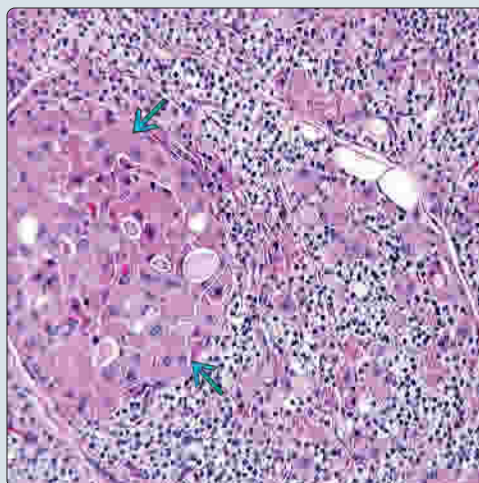


Intraparathyroid Paraganglioma

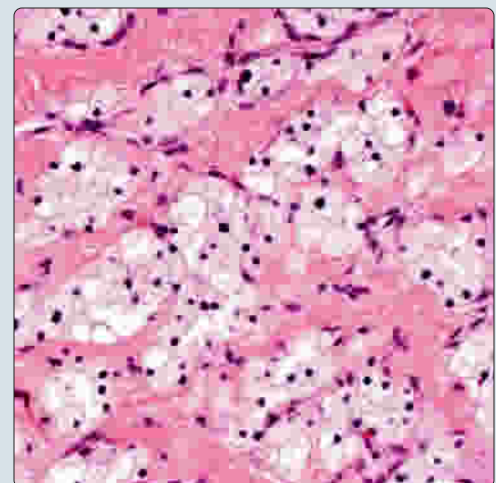


(Left) This is an example of metastatic thyroid follicular carcinoma (oncocytic type) to the parathyroid gland. There is a distinct "nodule" of tumor that is morphologically malignant, distinct from the surrounding parathyroid tissue. **(Right)** A clear cell parathyroid adenoma can morphologically mimic a metastatic clear cell renal carcinoma. However, the cytoplasm is slightly oxyphilic, and there are no pseudoalveolar erythrocyte collections.

Metastatic Thyroid Follicular Carcinoma



Clear Cell Neoplasm



TERMINOLOGY**Definitions**

- Tumors secondarily involving parathyroid gland as result of hematogenous/lymphatic spread from primary malignancies of distant sites
 - Direct extension from contiguous structures (larynx, trachea, pharynx, thyroid, esophagus, lymph nodes, neck soft tissues, mediastinum) is **excluded**
- Lymphomas and leukemias are excluded by definition

ETIOLOGY/PATHOGENESIS**Pathogenesis**

- Parathyroid gland is richly vascularized, but tends not to have high frequency of metastases
- Abnormal parathyroid tissue (hyperplasia, adenoma, carcinoma) seem to contain metastases more frequently than normal tissue
 - Alterations in vascularity or blood flow may contribute to metastatic disease development

CLINICAL ISSUES**Epidemiology**

- Incidence
 - Depends on underlying frequency of primary tumor
 - < 0.1% of parathyroid glands removed surgically
 - ~ 1% in autopsied patients with disseminated malignancies
- Age
 - All ages, but tendency in older patients
 - Mean: 7th decade
- Sex
 - Female > male (1.2:1)
 - Increased metastases of breast and gynecologic primaries compared to prostate primaries

Site

- Tends to involve more than 1 parathyroid gland

Presentation

- Vast majority of patients are asymptomatic
- Occasionally mass in neck
- Hyper- or hypoparathyroidism are exceptionally rare
- Primary site depends on age and gender
 - Carcinomas are most common
 - Breast (lobular > ductal), lung, kidney
 - Melanoma, soft tissue sarcomas
 - All anatomic sites are potential candidates
- Direct extension (larynx, thyroid, esophagus) may be seen
- Paraganglioma or soft tissue tumors rarely affect parathyroid tissue

Laboratory Tests

- Generally, no parathyroid hormone or calcium abnormalities
- Primary hyperparathyroidism may be present

Treatment

- Parathyroidectomy, especially if slow-growing tumor or isolated metastasis

Prognosis

- Usually poor outcome, determined by primary type
- Metastases to parathyroid gland correlate with poor prognosis
 - Seldom isolated parathyroid metastases: Usually extensive multiorgan metastases
- Management is usually symptomatic or palliative

MACROSCOPIC**General Features**

- Gland may be slightly enlarged, but tumor focus is not usually grossly apparent
- Direct extension may result in "attachment" to thyroid, larynx, or esophagus

Size

- Wide range, but vast majority are microscopic

MICROSCOPIC**Histologic Features**

- Features of primary tumor are usually maintained
- Lymphovascular location of tumor emboli
- If direct extension, tumor is usually large, incidentally encompassing parathyroid
- Secondary tumors have unique morphology, distinct from parathyroid

ANCILLARY TESTS**Immunohistochemistry**

- Metastatic tumors have unique immunohistochemical profiles, usually distinct from parathyroid primaries
 - Renal cell carcinoma **positive**: EMA, RCC, CD10, PAX8, CA9
 - Parathyroid carcinoma **positive**: EMA, RCC, CD10; **negative**: Parafibromin, CA9, PAX8

DIFFERENTIAL DIAGNOSIS**Clear Cell Adenoma**

- Distinct population of cells that compresses surrounding parathyroid parenchyma
- Lacks lymph-vascular invasion, vascular pattern, and extravasated erythrocytes

Medullary Carcinoma

- Tends to be plasmacytoid, with amyloid
- **Positive**: Calcitonin, CEA-M, TTF-1, chromogranin, synaptophysin, CD56

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